# Definitions

## ❖ Pharmaceutical Chemistry:

٧٠-٣٠

It is the study of the molecular and mechanistic aspects of pharmaceuticals.

Pharmaceutical chemistry is *the chemistry of drug design and development, drug action, drug transport, drug delivery, and targeting.*

The development of new pharmaceuticals is critically dependent on a molecular-level understanding of biological processes and mechanisms of drug action.

## ❖ Target :

**Cellular structure** ( macromolecule: receptor, enzyme, etc.) to which a drug binds yielding an effect.

المركب الرئيسي الذي تشتق منه المركبات أو نعمله تحور وتكون لنا مركبات اخرى

## ❖ Lead Compound :

A new compound which has been identified to have a desired pharmacological effect and from which analogues are synthesized.

→

## ❖ Molecular Modification :

Process in which analogs are synthesized in order to find a drug that might have improved therapeutic activity or fewer side effects.

51 في الامتحان مثلا حول الكوكائين الى بروكائين

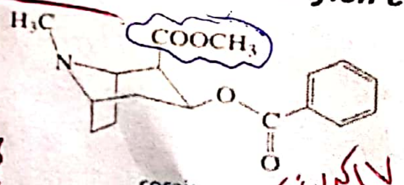
تم الاعداد بواسطة نجم الصوفي

سؤال امتحان

**Example 1 :**

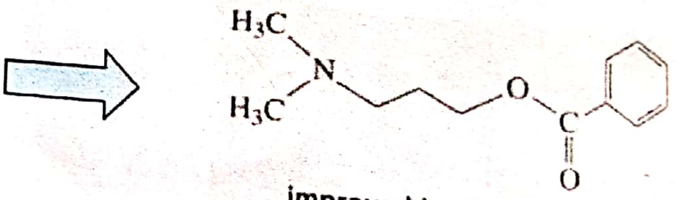
Cocaine "lead compound" which extracted from *Erythroxylon coca*

من اجل نمنع الوصول الى الدماغ نزيل مجموعة COOCH3 ونحذف الكربونات الزيادة وكمان نضيف NH2



cocaine
lead compound

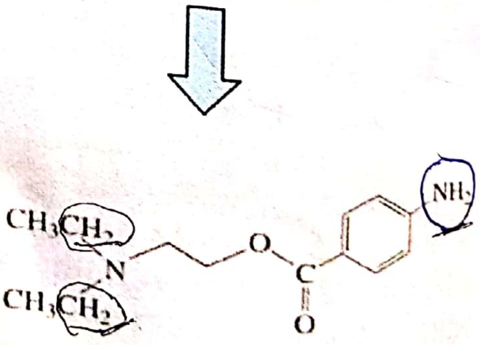
١٧ كربون



improved lead compound

❖Uses: used as local anesthetic

❖Side effects: C.N.S disturbing effect ( from initial euphoria to severe depression



procaine
Novocain

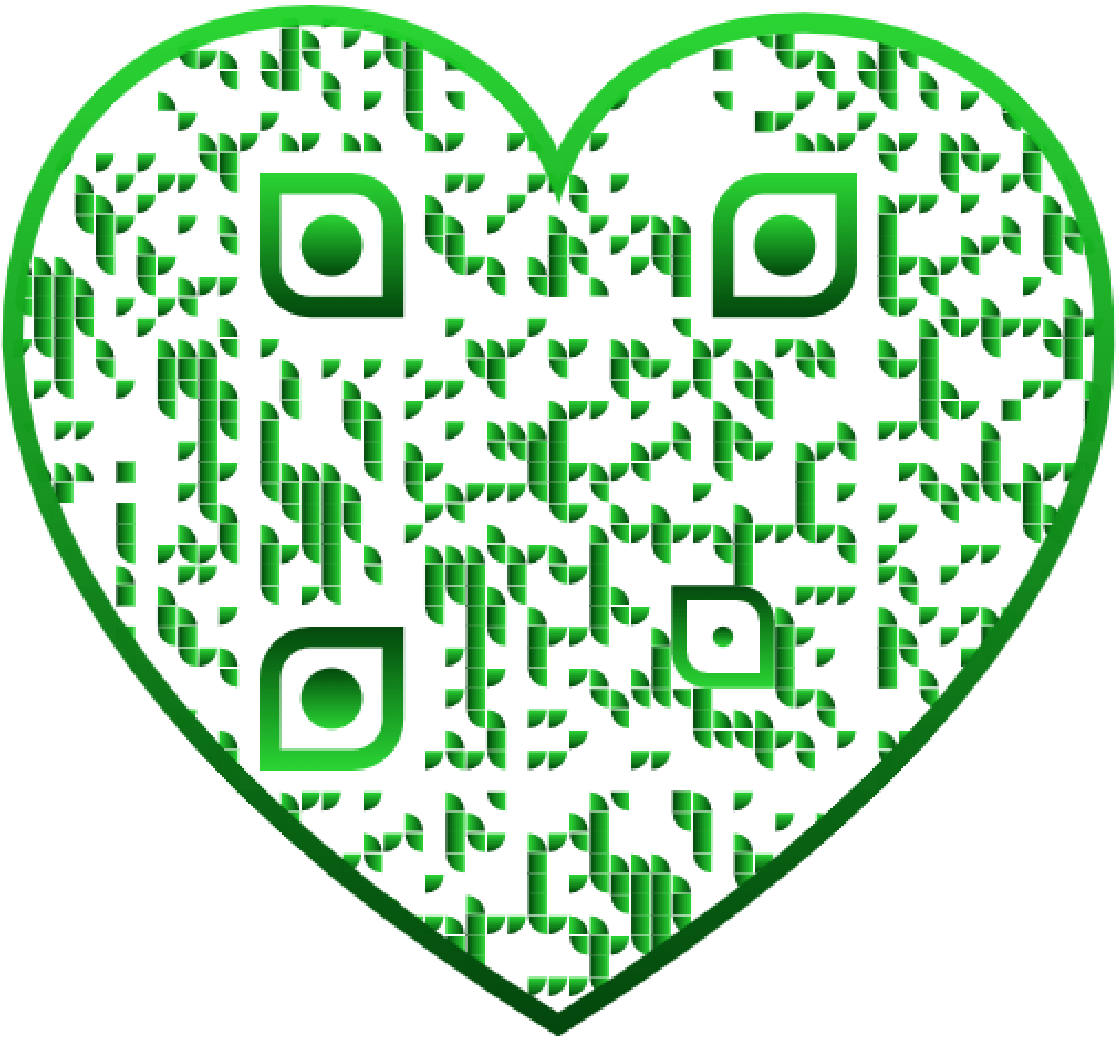
**Molecular modification was done by :**

ازالة مجموعة المثيل

لازالة الكربونات الزيادة

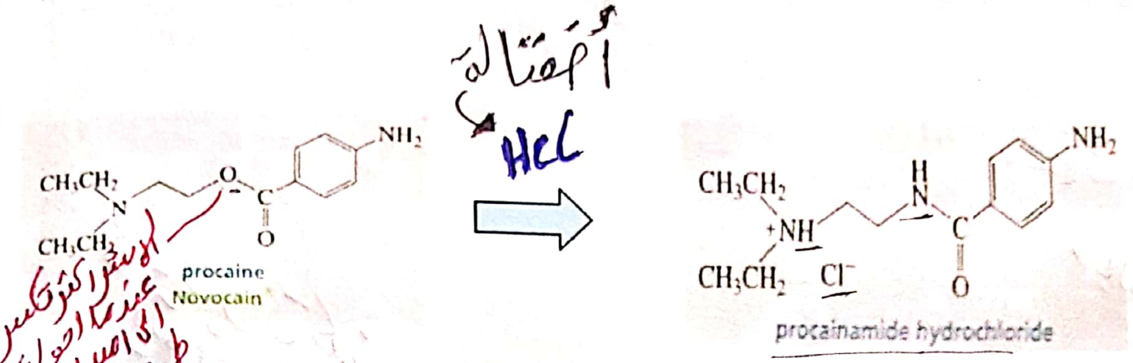
Removing the methoxycarbonyl group & cleavage of the seven membered ring compound with the same therapeutic effect but almost with no C.N.S disturbing effect "**procaine**".

اضافة NH2



Gocaine → procaine → procainamide HCl

**lead compound contt.**


CH₃CH₂
N
CH₃CH₂
O
C
O
NH₂
أمثالة
HCl
CH₃CH₂
⁺NH
CH₃CH₂
Cl⁻
H
N
C
O
NH₂

procaine
Novocain

procainamide hydrochloride

الاستر اكثر تكسير عندما احوله الى اميد يصبح طول المفعول

- By further replacing the ester linkage of procaine by an amide linkage

'Compound which is clinically used as an antiarrhythmic " procainamide HCl "'

المورفين معه HO كحول و HO فينول اذا عملت ميثيليشن للـ OH حق الفينول يتحول الى كودائين

بينما اذا عملت ~~ميثيليشن~~ للـ HO الاثنين يتحول الى هيروين.

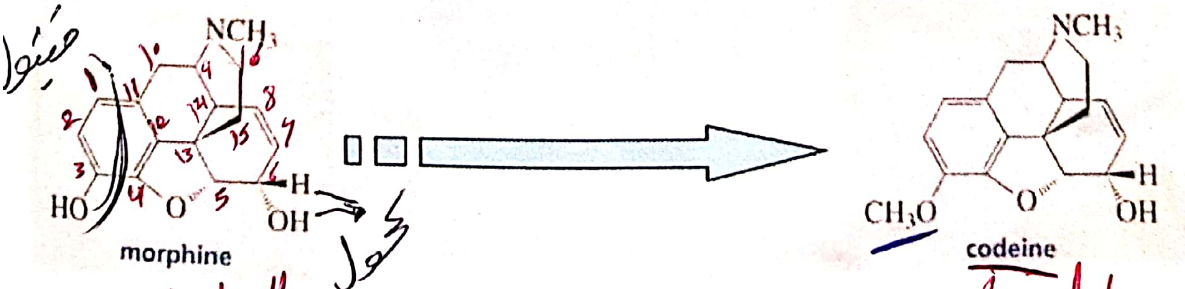
~~Acyl~~ acetylation [illegible]

**Example 2 :**

**Morphine** "lead compound" which extracted from *Papaver somniferum*

- **Uses:** Pain killer
- **Side effects :** respiratory depression , addiction أدمان

➢Methylation of one of the OH groups lead to 'codeine' which is used as cough sedative (antitussive).


فينول
NCH₃
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
HO
O
H
OH
يتحول
NCH₃
CH₃O
O
H
OH

morphine

codeine

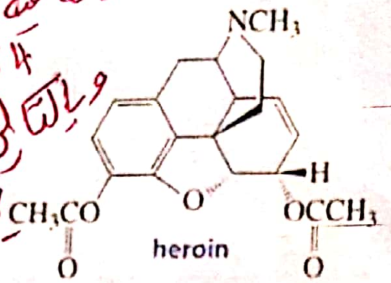
- pain Killer
- respiratory depression

cough sedative (antitussive)

# Lead compound contt..

➤Acetylation of both OH groups of morphine lead to heroin which is more potent
then morphine WHY?

لأنه فيه كربونات زيادة 4 كربونات وبالتالي يدخل CNS بسرعة وتأثيره أقوى


heroin

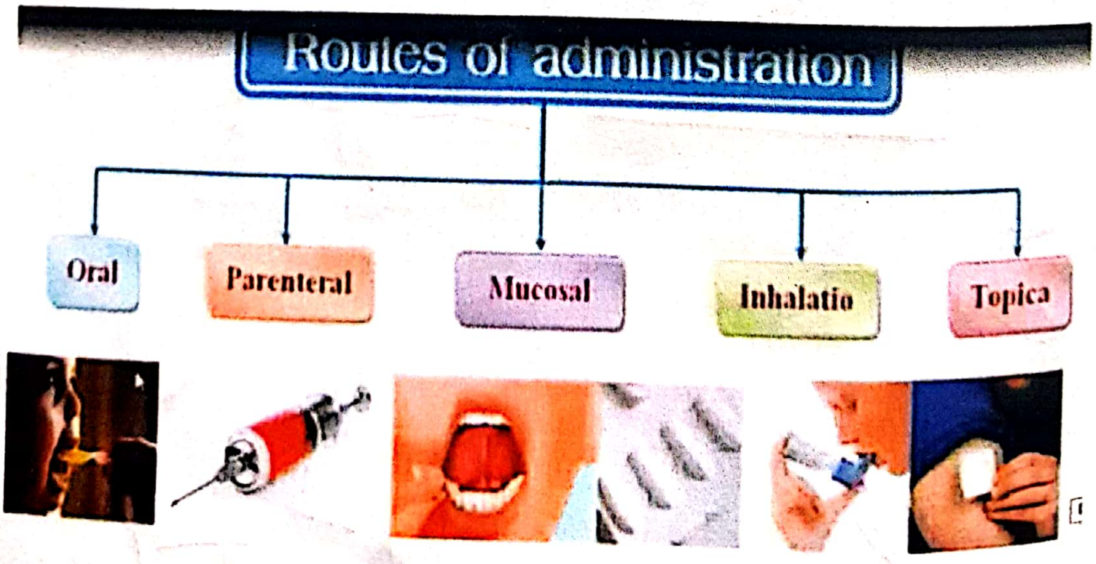
Drug enforcement agencies use trained dogs to recognize the pungent odor of acetic acid

في المطارات كيف تتعرف الكلاب انه في هيروين داخل الشنطة؟

يتم تعريف الكلاب على رائحة الخل " $CH_3COOH$ " لأن الهيروين يوجد فيه 2 هذه المجموعات تتكسر بالرطوبة والحرارة لأنها عبارة عن استر وبالتالي يعرف الكلب

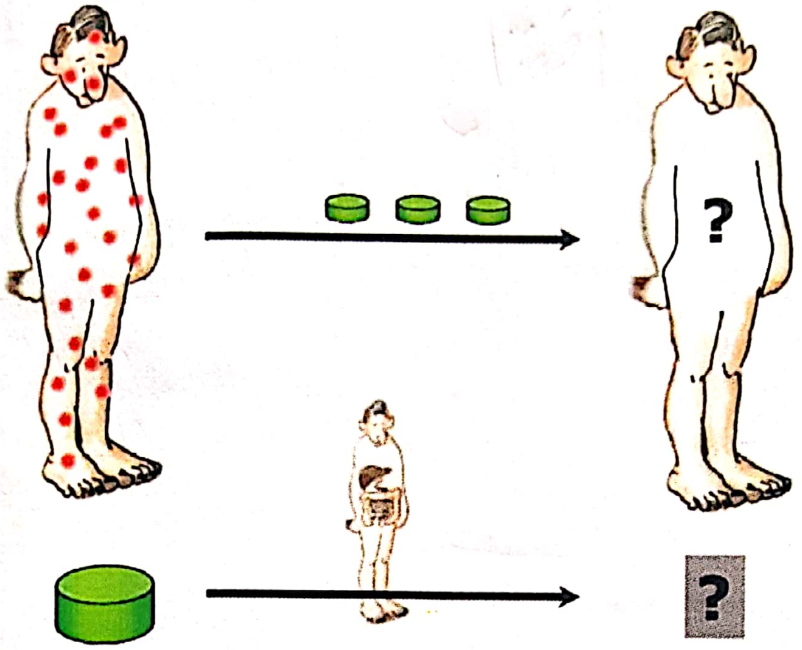
## Routes of administration

Physico-chemical properties [partition coefficient, dissociation constant, steric factor, solubility,…] → affect pharmacokinetic of the drug [its movement in body → ADME



** One drug can be superior to another just because it has good ADME, rather than good interaction with its target

## Pharmacokinetics vs. pharmacodynamics



**PD – What does the drug to the body ?**

**PK – What does the body to the drug ?**

ما الذي يفعل الجسم بالدواء

**Pharmacokinetics**
What the body does to the drug

ADME

**A**bsorption
**D**istribution
**M**etabolism
**E**limenation

**Pharmacodynamics**
What the drug does to the body

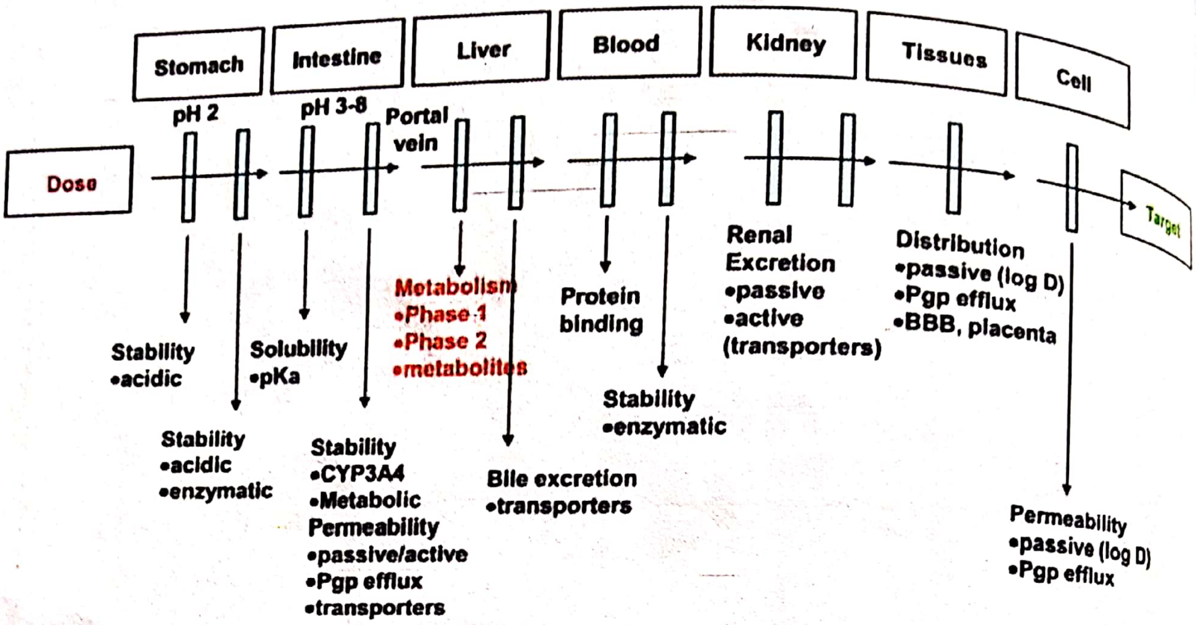
Mechanism of action
(Drug receptor interaction)

**Pharmacotherapeutics**
The result of drug and body action

Uses of drug
(Therapeutic effect)

# Pharmacokinetic processes

## Barriers from Dosing to the Therapeutic Targets



Dose

Stomach
pH 2

Stability
•acidic

Stability
•acidic
•enzymatic

Intestine
pH 3-8

Solubility
•pKa

Stability
•CYP3A4
•Metabolic
Permeability
•passive/active
•Pgp efflux
•transporters

Liver
Portal vein

Metabolism
•Phase 1
•Phase 2
•metabolites

Bile excretion
•transporters

Blood

Protein binding

Stability
•enzymatic

Kidney

Renal Excretion
•passive
•active
(transporters)

Tissues

Distribution
•passive (log D)
•Pgp efflux
•BBB, placenta

Cell

Permeability
•passive (log D)
•Pgp efflux

Target

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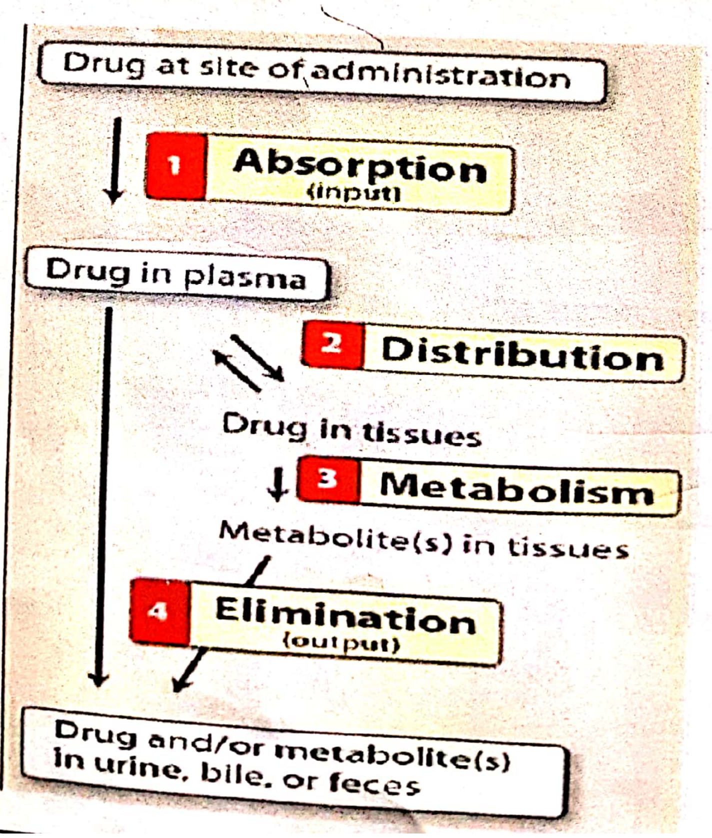
# Pharmacokinetics



Drug at site of administration

1 **Absorption** (input)

Drug in plasma

2 **Distribution**

Drug in tissues

3 **Metabolism**

Metabolite(s) in tissues

4 **Elimination** (output)

Drug and/or metabolite(s) in urine, bile, or feces

# Routes of administration

## 1) Parentral

- I.V, intra-arterial, intra-spinal → No absorption barrier
- I.M, S.C, intra-dermal, intra-peritoneal → drug pass some membrane barriers till reaching circulation.

## 2) GIT

- 1st, the drug must dissolute

↓

Then absorption.

- This is affected by:

① [i] pH of the part of GIT from which drug absorbed [somach → 1-3.5 / duodenum → 6-7 / lower ileum → 8].

② [ii] Dissociation rate of the drug at that pH.

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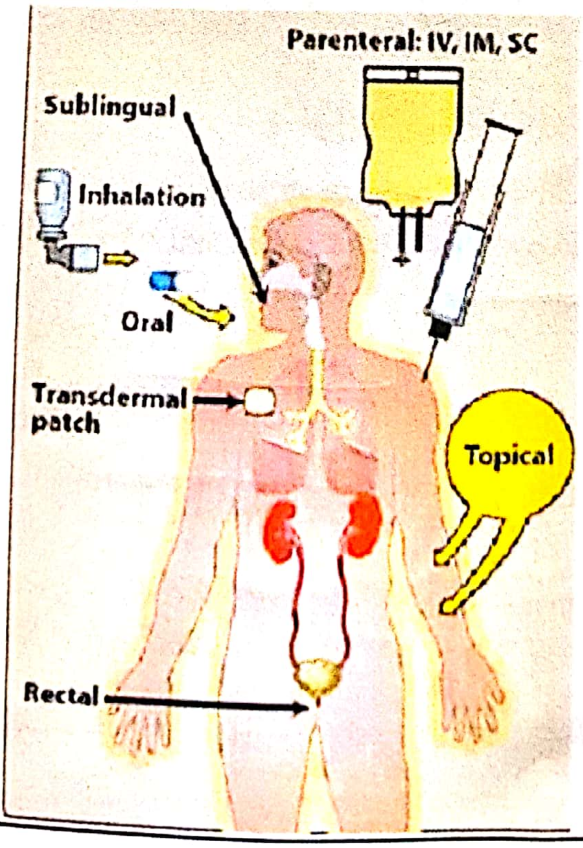
# Routes of Drug Administration


Parenteral: IV, IM, SC
Sublingual
Inhalation
Oral
Transdermal patch
Topical
Rectal

# Drug Dissolution

It's the solubility of the drug in the fluids of the GIT, it depends on:

## (1) Particle size:

- ↓ Particle size → ↑ surface area exposed to fluids of GIT → ↑ dissolution. ↑ absorption

- Spironolactone, Griseofulvin → formulated as micronized form to improve bioavailability

## (2) pH of the medium:

solubility

- *Weakly acidic drugs* → dissolved in alkaline region of GIT.

*Weakly basic drugs* → dissolved in acidic region of GIT.

# Drug Absorption

After being dissolved in GIT → pass membrane of GIT → circulation.
This occurs by:

## (1) Active Transport OR Carrier mediated transport:

- *Energy is required* → transport is against concentration gradient [from ↓ to ↑].

There should be *structural similarity* between the drug & the substrate normally carried across the membrane.

## (2) Passive Diffusion:

- Movement of drug *follow concentration gradient* [from ↑ to ↓]
- Rate of diffusion is proportional to the drug concentration at site of absorption.

$$\boxed{-\frac{dC}{dt} = KC_1}$$

($dC/dt$ → rate of diffusion)
($C_1$ → concentration of drug at site of absorption)
($K$ → constant depending on *area* & *thickness* of membrane & *partition coefficient* of the drug)

## (3) Convective absorption:

For small molecules of molecular radius less than 4 A° pass through water filled pores in the biological membrane.

### ❖ Factors affecting simple diffusion:-

1: **Dose concentration** (*Increase* dose concerntration →*Increase* absorption)

2: **Molecular weight & size** (*Increase* Mwt. → *Decrease* absorption).

3: **Ionization** (*Water soluble* drug (Ionized) → *Decrease* absorption).

4: **PH at the site of absorption.**

- Most of drugs are weak acids or weak bases

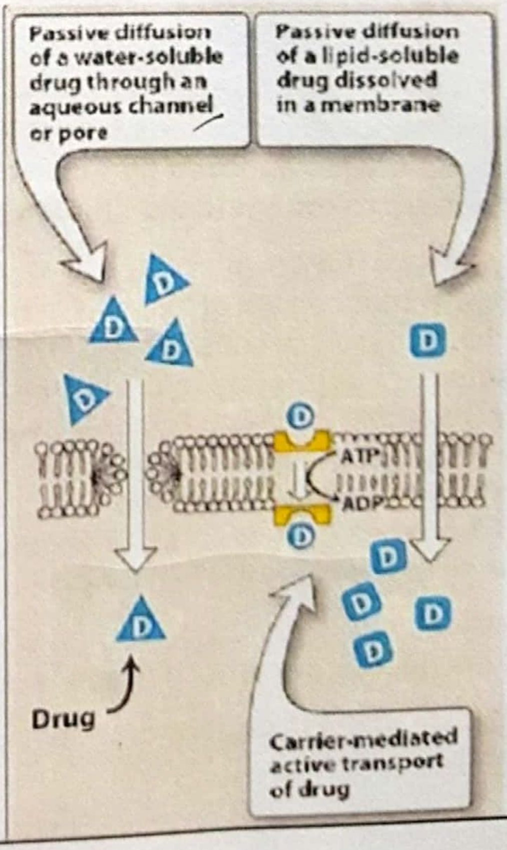
*Weak acid drugs* → less ionized in *acidic* medium → *decrease* ionization → *Increase* Absorption

*Weak base drugs* → less ionized in *basic* medium → *decrease* ionization → *Increase* Absorption

- weak acid drugs in acidic medium → more absorption
- weak base drugs in basic medium → more absorption

## Absorption of Drugs

### Transport of a drug from the GI tract


Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
D
ATP
ADP
Drug
Carrier-mediated active transport of drug

## Factors affecting absorption of drugs:-

**1: Patient-Related factors:**

- **Route of administration** → IV > IM > SC > Oral > Skin
- **Absorbing surface** → *Increase* surface → *Increase* absorption.
- **Systemic circulation** → Shock and heart failure → *decrease* absorption.
- **Presence of other drugs** → Adrenaline SC → Vasoconstriction (VC) → ↓ absorption.
- **Specific factors** → E.g. intrinsic factor for Vit.B12.

**2: Drug-Related factors:**

- **Lipid solubility** → High lipid solubility drug → High absorption.
- **Ionization** → Non-ionized drugs → High absorption.
- **Valency** → Ferrous iron ($Fe^{2+}$) absorbed more than ferric iron ($Fe^{3+}$).
- **Nature** → Inorganic (small molecules) > Organic (Big molecules).
- **Pharmaceutical preparation** → Solution > Suspension > Tablet
- **PH of the drug**
  - Most of drugs are weak acid or weak base, the ionization of drugs may markedly reduce their ability to permeate membrane.
  - The degree of ionization drugs are determined by the surrounding pH on their $pK_a$.
  - Acidic drug are largely unionized in stomach and absorbed faster, while basic drug are absorbed faster in intestine.

## Factors that influence bioavailability

1) **First-pass hepatic metabolism:** When a drug is absorbed across the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized by the liver, the amount of unchanged drug that gains access to the systemic circulation is decreased.

2) **Solubility of the drug:**
Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes
drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in aqueous body fluids
.For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions.
drugs that are highly lipid-soluble, and they are transported in the aqueous solutions of the body on carrier proteins such as albumin.

3) **Chemical instability:** Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin,

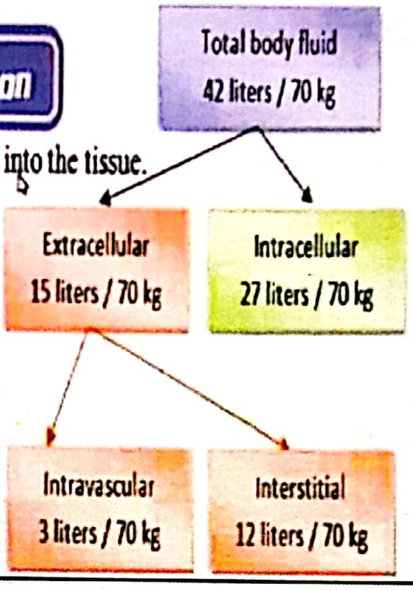
4) **Nature of the drug formulation:** (such as binders and dispersing agents)

***Henderson Hasselbalch equation*** (Determination degree of ionization)

For weak acid drugs: $pK_a$ = log Unionized form / Ionized form

For weak base: $pK_a$ = log ionized form / unionized form

## 2: Distribution


Total body fluid 42 liters / 70 kg

Extracellular 15 liters / 70 kg

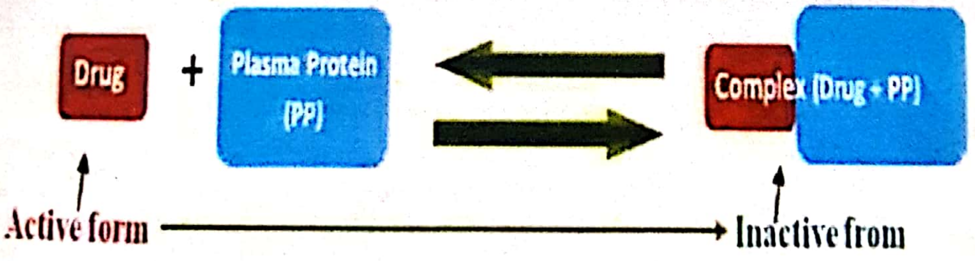
Intracellular 27 liters / 70 kg

Intravascular 3 liters / 70 kg

Interstitial 12 liters / 70 kg

- **Def.→** The transfer of drug from the blood stream into the tissue.
- **Depend on :-**
  - *Increase* blood flow → *Increase* distribution (Lung > Liver > Brain)
  - Ability of the drug to pass biological membrane (Polarity and size of drug)
  - Degree of binding to plasma protein (PP) (*Increase* PP binding → *decrease* distribution)

## Binding to plasma proteins



Active form → Inactive from

- When the free drug concentration is decreased → the binding drug converted to free drug → to give the same action.

***-Amount of free drug can be increase by:-***

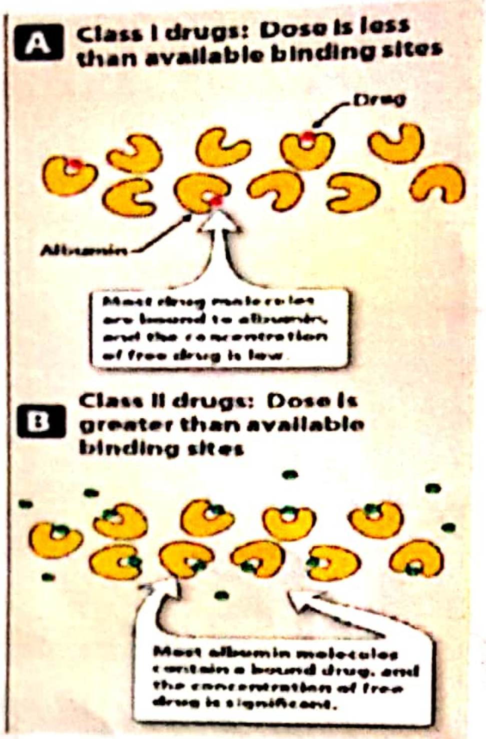
1: Displacement by other drugs→ Replacement of one drug by another.

→E.g. Aspirin and Warfarin (Anticoagulant) →Aspirin displaces warfarin due to high affinity to PP → increase free active Warfarin → Increase toxicity of warfarin.

- Drugs with high affinity for PP are Aspirin, Sulfonamides and Chloramphinicol can replace the other drugs e.g. Wafrarin.

2: Decrease in albumin or plasma protein → Liver disease.

# the degree of binding of the drug to plasma

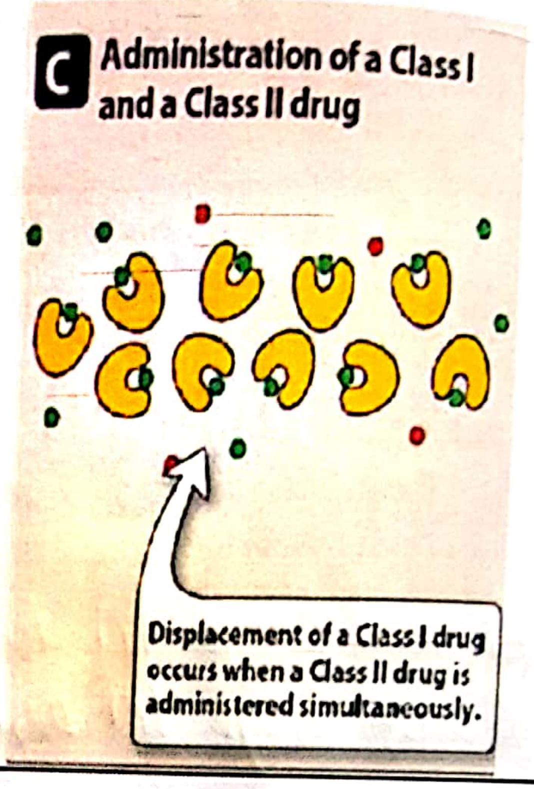


**A** Class I drugs: Dose is less than available binding sites

Most drug molecules are bound to albumin, and the concentration of free drug is low.

**B** Class II drugs: Dose is greater than available binding sites

Most albumin molecules contain a bound drug, and the concentration of free drug is significant.



**C** Administration of a Class I and a Class II drug

Displacement of a Class I drug occurs when a Class II drug is administered simultaneously.

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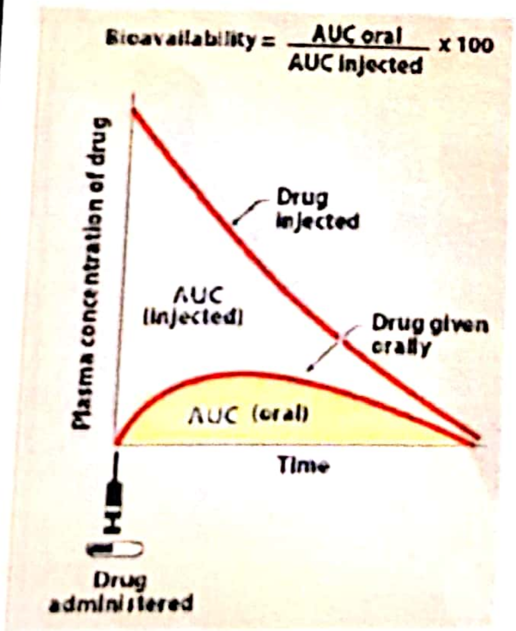
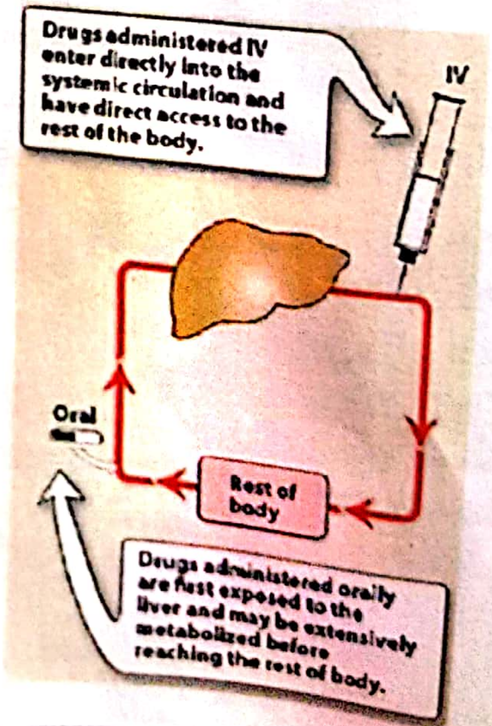
# Bioavailability



$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \times 100$$



Drugs administered IV enter directly into the systemic circulation and have direct access to the rest of the body.

Drugs administered orally are first exposed to the liver and may be extensively metabolized before reaching the rest of body.

## Sites of loss:

•Relatively little amount of the absorbed drug reaches its target. This is because the drugs encounter many *sites of loss*

*•such as*

*•protein binding*

*• metabolism,*

*•excretion and*

*•storage sites*

•The distribution between the site of action and sites of loss is dependent on the physicochemical properties of the drug.

## Sites of loss:

1] Protein binding:

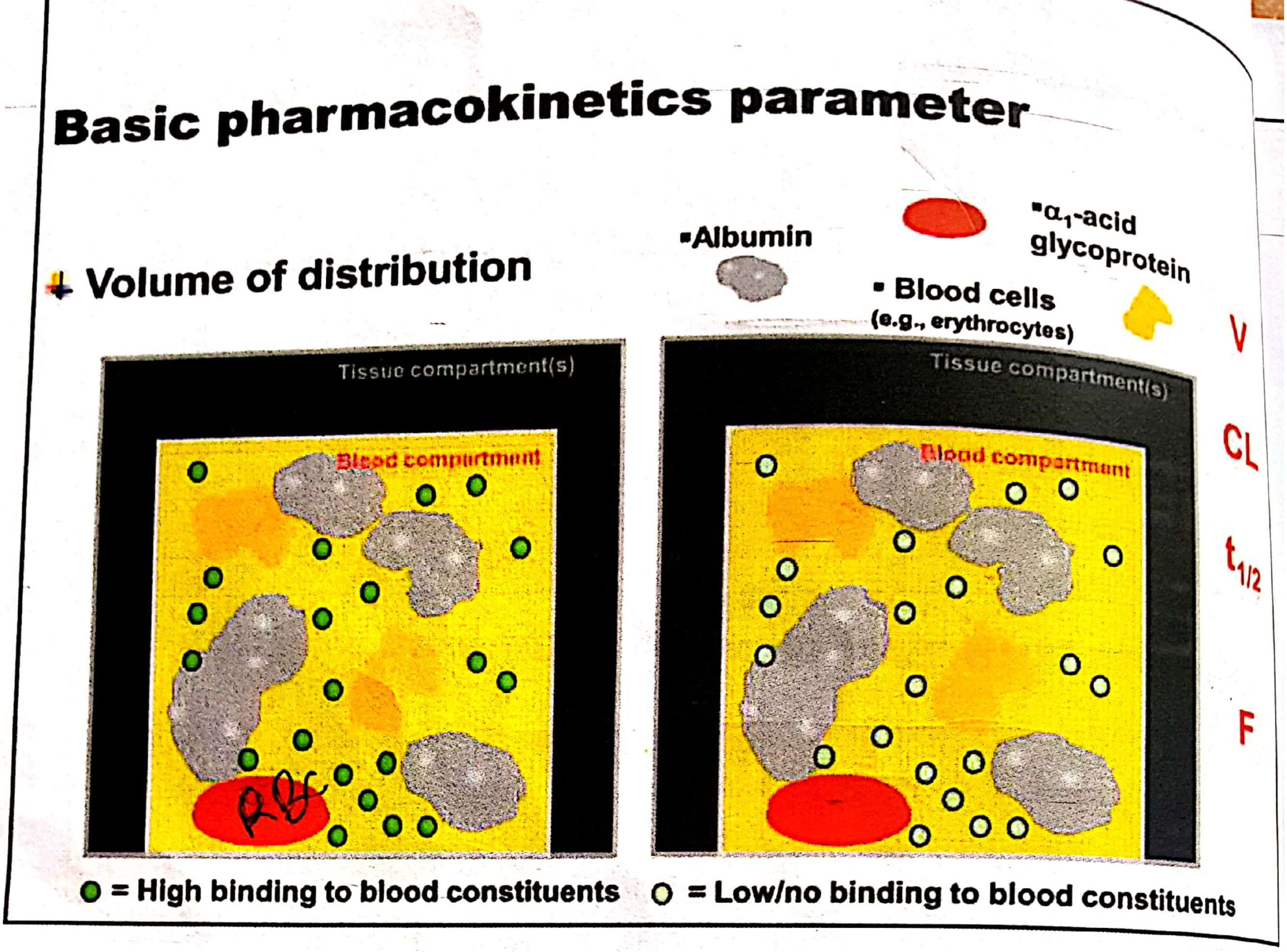
•Binding with plasma proteins(serum albumine, acid glycoprotein,lipoprotein) depend on the chemical structure(weak or strong acid or base or neutral).

•The most significant protein involved in the binding of drugs is albumin, which comprise more than half of all blood proteins,albumine can interact e acidic or basic drug, acid glycoproteininteracts e basic drug s while lipoprotein bin e basic and neutral drugs

•The bound drug is a large complex incapable of performing any biological process [no metabolism, no excretion, no interaction with receptor..].

•So the plasma protein binding can be regarded as storage site for the drug from which the drug is gradually released according to the equilibrium existing between the free and bound drug.

•In some cases, it contributes for long duration and protection from rapid metabolism.



## Basic pharmacokinetics parameter

- Volume of distribution

- Albumin
- α₁-acid glycoprotein
- Blood cells (e.g., erythrocytes)

● = High binding to blood constituents
○ = Low/no binding to blood constituents

Tissue compartment(s)
Blood compartment
RBC
Tissue compartment(s)
Blood compartment

V

CL

$t_{1/2}$

F

### 2] Neutral fat:

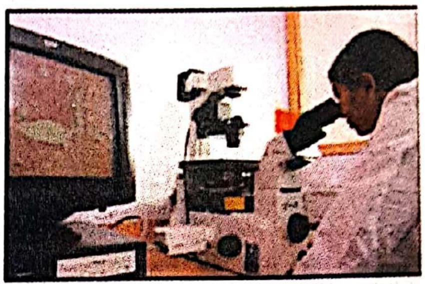
•Deposition into adipose tissue depends on log p and pKa, so lipophilic drugs are stored in fat tissues and then they will eventually be released into circulation to exert their action.

### 3] Excretion:

•Drugs of suitable size to pass glomerular membranes and that are soluble enough in aq. medium at pH of the urine → excreted.

### 4] Metabolism.

## Activity is just the beginning



- Dissolution
- Stomach
- Intestinal Enzymes
- Absorption
- Liver (Metabolism)
- Protein Binding
- Blood Brain Barrier
- Cellular Penetration
- Target
- Excretion

**Drug gauntlet**

One needs to show the drug gets where it should and DOES NOT DO ANYTHING ELSE BAD.

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# Advanced Medicinal Chemistry

## Physical Properties and Drug Design

# Overview

- Introduction
- Ionisation
- Lipophilicity
- Hydrogen bonding
- Molecular size
- Rotatable bonds
- Bulk physical properties
- Lipinski Rule of Five
- The Drug Design Conundrum

**Physical Properties and Drug Design**

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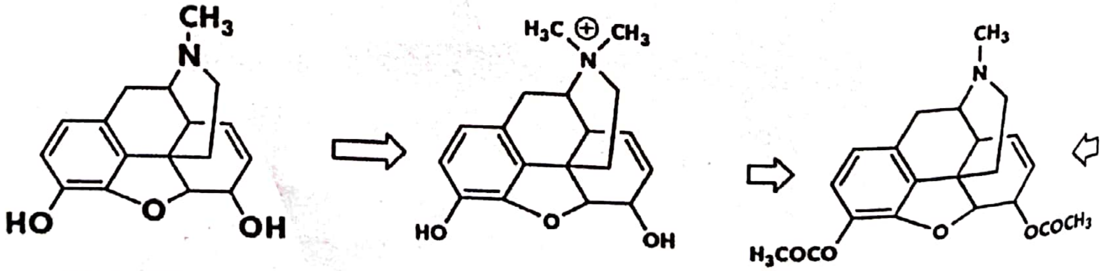
# Physico-Chemical Properties
## Introduction

**Chemical structure of organic compounds→ very important in determination of their physical properties & biological activity**

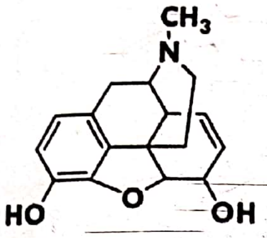
**Any minor change in chemical structure → may lead to dramatic change in activity [affect polarity, crossing BBB(blood brain barrier), binding to receptor.....]. Example**



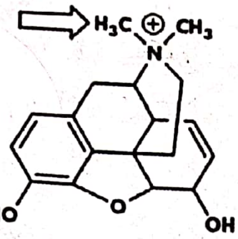
Morphine (active)

Inactive derivative

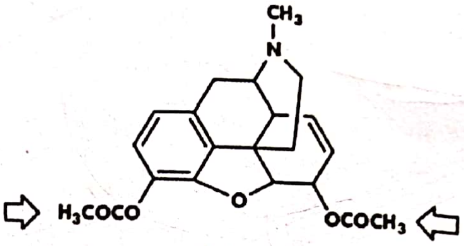
Heroin (more potent)



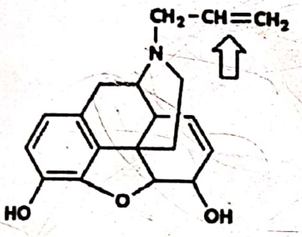
**Morphine**
**(active)**



Inactive derivative



**Heroin**
**(more potent)**

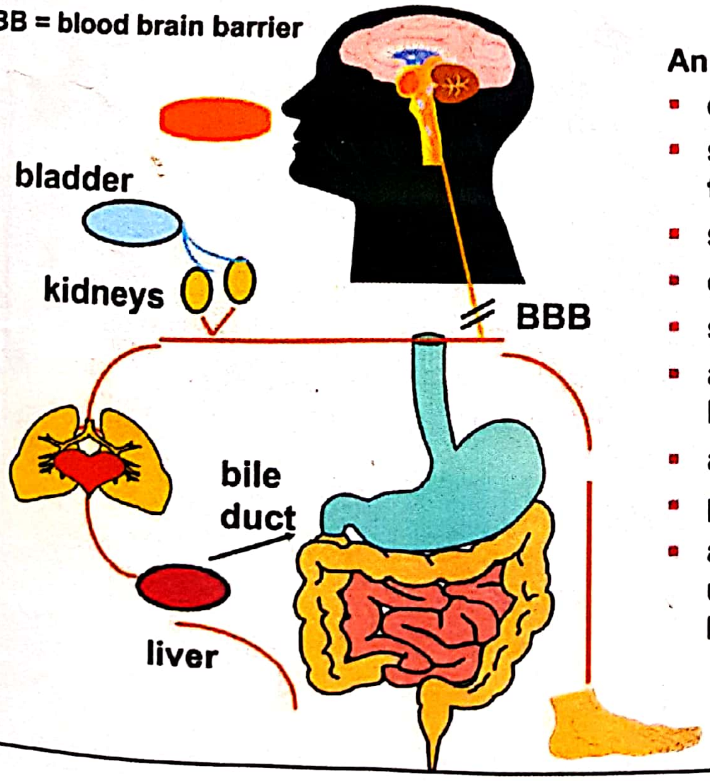


**Nalorphine**
**(antagonist)**

## What must a drug do other than bind?

A drug needs to be able to do many things other than bind to the active site of the receptor!

BBB = blood brain barrier



An oral drug must be able to:

- **dissolve**
- **survive a range of pHs (1.5 to 8.0)**
- **survive intestinal bacteria**
- **cross membranes**
- **survive liver metabolism**
- **avoid active transport to bile**
- **avoid excretion by kidneys**
- **partition into target organ**
- **avoid partition into undesired places (e.g.** brain, foetus)

# Ionisation

- Ionisation = protonation or deprotonation resulting in charged molecules
- About 85% of marketed drugs contain functional groups that ar ionised to some extent at physiological pH (pH 1.5 – 8).

**The acidity or basicity of a compound plays a major role i controlling:**

- Absorption and transport to site of action
  - Solubility, bioavailability, absorption and cell penetration, plasma binding, volume of distribution
- Binding of a compound at its site of action
  - un-ionised form involved in hydrogen bonding
  - ionised form influences strength of salt bridges or H-bonds
- Elimination of compound
  - Biliary and renal excretion
  - CYP $P_{450}$ metabolism

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# Ionisation

❖Drugs are only **absorbed passively** when they are **unionised.** This is because the compound has to pass through **a lipophilic** ('fat loving') membrane and this process will be unfavourable **for charge molecules.**

غير مرغوب بها

❖In a more **acidic medium**, such as the **stomach, the percentage ionised for an acidic** compound will be less than at pH 7.4 and so more **compound** will have the capacity to **be passively absorbed.**

❖**In comparison**, a **basic compound** in an **acidic medium** will be **more ionised** and **so less of the compound will** be in the **neutral form** and have **the capacity** to **undergo passive absorption.**

❖**Weak acid at acidic pH** : **more lipid-soluble**, because it is uncharged—the **uncharged** form more readily **passes** through **biological membranes**.
Note that a **weak acid** at **acidic pH** will pick up a proton and become **uncharged**
$RCOO^- + H^+ \rightarrow RCOOH$

❖**Weak base** at **alkaline pH**: **more lipid-soluble**, because it is uncharged—the **uncharged** form more readily **passes through biological** membranes.
Note that a weak base at more **alkaline pH** will lose a proton, becoming **uncharged**
$RNH_3^+ \rightarrow RNH_2 + H^+$

---

## How does pH vary in the body?

| Fluid | pH |
|---|---|
| Aqueous humour | 7.2 |
| Blood | 7.4 |
| Colon | 5-8 |
| Duodenum (fasting) | 4.4-6.6 |
| Duodenum (fed) | 5.2-6.2 |
| Saliva | 6.4 |
| Small intestine | 6.5 |
| Stomach (fasting) | 1.4-2.1 |
| Stomach (fed) | 3-7 |
| Sweat | 5.4 |
| Urine | 5.5-7.0 |

So the same compound will **be ionised to different** **extents in different parts of the body.**

This means that, for example, **basic compounds** will **not be so well absorbed** in the **stomach** than acidic compounds

- **Weak acid at acidic pH** : **more lipid-soluble**, because it is uncharged—the **uncharged** form more readily **passes** through **biological membranes**.

Note that a **weak acid** at **acidic pH** will pick up a proton and become **uncharged**

RCOO–+ H +→RCOOH

- **Weak base** at **alkaline pH**: **more lipid-soluble**, because it is uncharged—the **uncharged** form more readily **passes through biological** membranes.

Note that a weak base at more **alkaline pH** will lose a proton, becoming **uncharged**

RNH3+→RNH2+ H+

---

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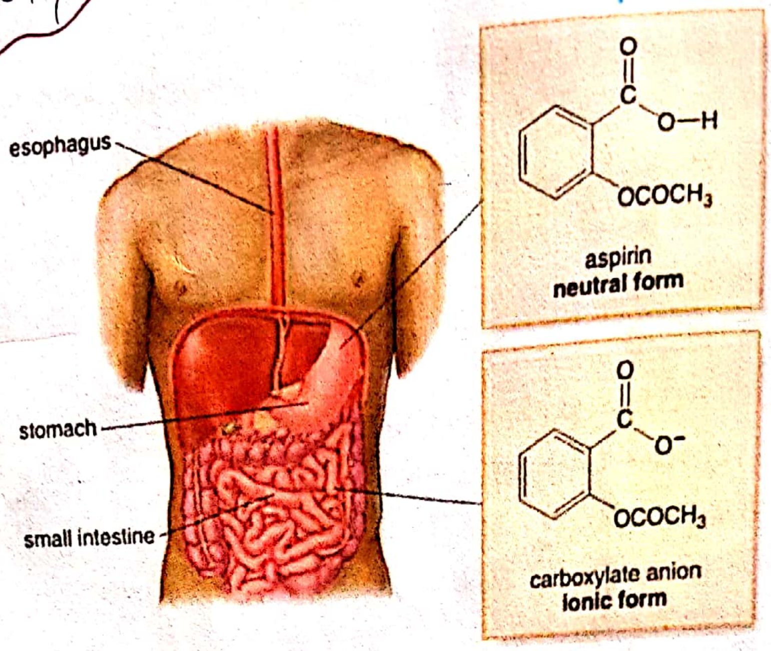
So the same compound will **be ionised to different** **extents in different parts of the body.**

This means that, for example, **basic compounds** will **not be so well absorbed** in the **stomach** than acidic compounds

سؤال في الامتحان

Passage through the cell membrane occurs in the neutral form.


esophagus
stomach
small intestine
O
C
O—H
OCOCH3
aspirin
neutral form
O
C
O−
OCOCH3
carboxylate anion
ionic form

In the stomach, aspirin exists as a neutral organic compound.

In the intestines, aspirin exists as an ionic compound.

---

# Ionisation constants or Dissociation Constant (pKa)

- The equilibrium between un-ionised and ionised forms is defined by the acidity constant $K_a$ or $pK_a = -\log_{10} K_a$
- For an acid:

$$HA \overset{K_a}{\rightleftharpoons} H^+ + A$$

$$K_a = \frac{[H^+][A^-]}{[AH]}$$

- For a base:

$$BH^+ \overset{K_a}{\rightleftharpoons} H^+ + B$$

$$K_a = \frac{[H^+][B]}{[BH^+]}$$

When an acid or base is 50% ionised:

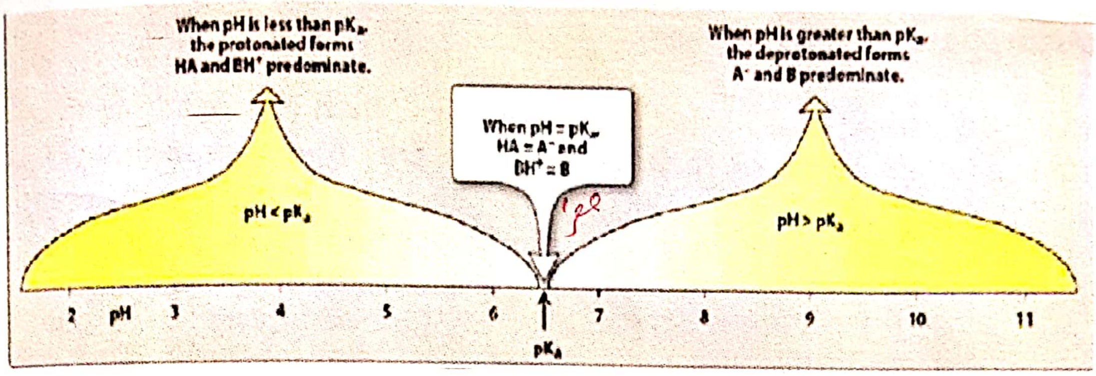
$$\boxed{pH = pK_a}$$

pKa = -log ka

# Dissociation Constant (pKa)

**For acids:** $RCOOH \rightleftharpoons RCOO^- + H^+$

$$pKa = pH + \log \frac{\text{Unionized acid}}{\text{Ionized acid}} = pH + \log \frac{RCOOH}{RCOO^-}$$


When pH is less than pKa, the protonated forms HA and BH+ predominate.
When pH = pKa, HA = A⁻ and BH+ = B
When pH is greater than pKa, the deprotonated forms A⁻ and B predominate.
pH < pKa
pH > pKa
2
pH
3
4
5
6
7
8
9
10
11
pKA

# Dissociation Constant (pKa)

## For bases:

$$pKa = pH + \log \frac{\text{Ionized base}}{\text{Unionized base}} = pH + \log \frac{RNH_3^+}{RNH_2}$$

اي شكل لا ايوني يكون ذائبا بالدهون ويكون شكل ممتص

- **Unionized form** → **lipid soluble** → **absorbable form.**

Ahmed

So, **weak acids** will exist in the **stomach** mostly in the **unionized** form so they are mainly **absorbed from stomach** [acidic]

**Weak bases** will exist in the **small intestine** mostly in the **unionized form** so they will be **absorbed mainly from intestine** **[basic].**

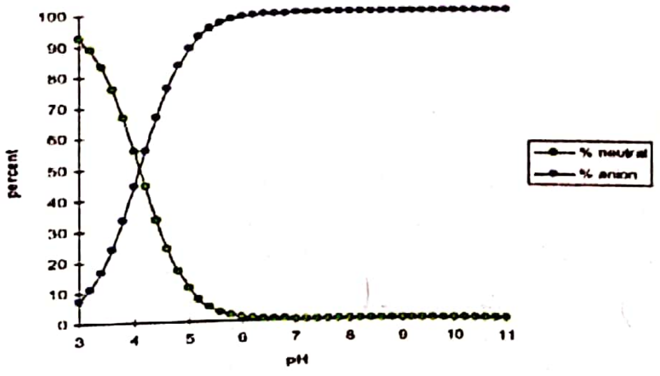
❖**The extent of ionisation of a compound can have a large effect on many biological properties**, such as

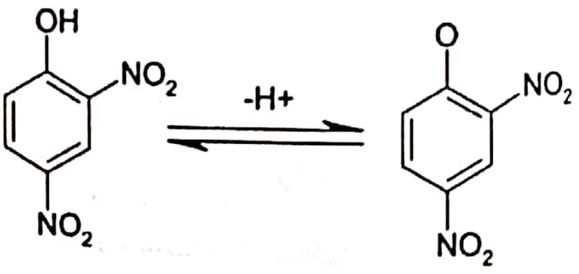
- ❖receptor/enzyme binding,
- ❖binding to plasma proteins,
- ❖ CNS penetration,
- ❖solubility
- ❖and absorption.

Once the **pKa value** of a **molecule is known**, then it is possible to calculate the **proportion of ionised** and **neutral species** at any pH.

---

# Ionisation of an acid – 2,4-dinitrophenol

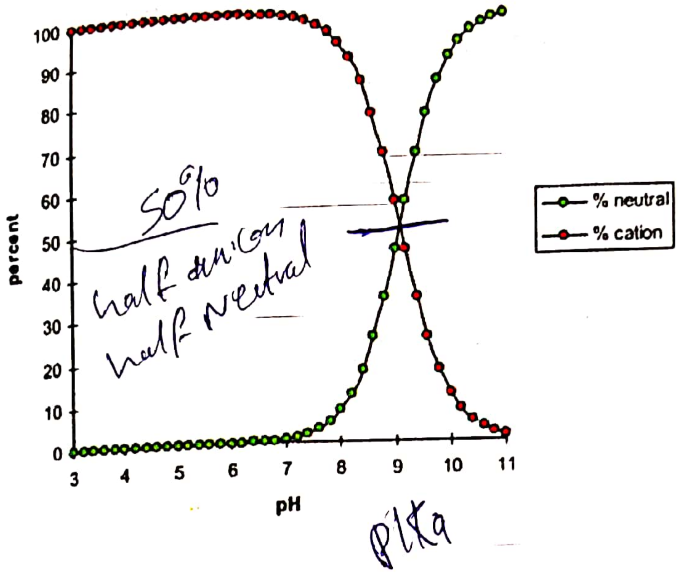




$pK_a = 4.1$

This diagram shows the proportions of phenol and phenolate anion at pHs between 3 and 11. **Above about pH 6** the phenol is completely **deprotonated.** When the pH is the same as **the pKa (i.e. 4.1 in this case), half the molecules are ionised** and **half are not**. Note that phenols are significantly more acidic than aliphatic alcohols, and that 2- and 4-nitrophenols are more acidic than phenol itself

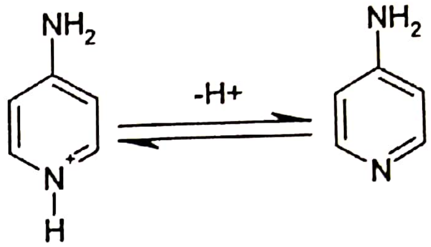
# Ionisation of an base – 4-aminopyridine



50%

half anion
half neutral

pKa



$pK_a = 9.1$

---

# Dissociation Constant (pKa)

***There's always equilibrium between unionized & ionized forms of the drug***

في الامعاء

| | | pKa | % absorbed at pH 1 | % absorbed at pH 8 |
|---|---|---|---|---|
| **Acids** | **5-nitro salicylic acid** | 2.3 | 52 | 16 |
| | **Salicylic acid** | 3 | 61 | 13 |
| | **Thiopental** | 7.6 | 46 | 34 |
| **Bases** | **Quinine** | 8.4 | 0 | 18 |
| | **Dextromethorphan** | 9.2 | 0 | 16 |

- When part of **unionized part** is absorbed, some **ionized forms converted into unionized** forms to **restore equilibrium. The** latter will absorbed & soon.

# Lipophilicity

Lipophilicity ('fat-liking') is the most important physical property of a drug in relation to its absorption, distribution, potency, and elimination.

Lipophilicity is often an important factor in all of the following, which include both biological and physicochemical properties:

effect on Pharmacodynamic & pharmacokinetics

- Solubility
- Absorption
- Plasma protein binding
- Metabolic clearance
- Volume of distribution
- Enzyme / receptor binding
- Biliary and renal clearance
- CNS penetration
- Storage in tissues
- Bioavailability
- Toxicity

---

# The hydrophobic effect

This principle also applies to the physical properties of drug molecules.

If a compound is **too lipophilic**, it may

- **be insoluble in aqueous media** (e.g. gastrointestinal fluid or blood)
- **bind too strongly to plasma proteins** and therefore the free blood concentration will be too low to produce the desired effect
- **distribute into lipid bilayers** and be unable to reach the inside of the cell

Conversely, if the compound is **too polar**, it may **not be absorbed** through the gut wall due **to lack of membrane solubility**.

So it is important that the **lipophilicity of a potential drug** molecule **is correct.**

## How can we measure this?

# Partition coefficients

$$X_{aqueous} \overset{P}{\rightleftharpoons} X_{octanol}$$

**Partition coefficient P** (usually expressed as $\log_{10}P$ or logP) is **defined as:**

$$P = \frac{[X]_{octanol}}{[X]_{aqueous}}$$

**P is a measure** of the relative **affinity of a molecule** for the **lipid and aqueous phases in the absence of ionisation.**

8(C) 16H

1-**Octanol** is the most frequently used **lipid phase** in pharmaceutical research. This is because:

- It has **a polar and non polar region** (like **a membrane phospholipid**)
- $P_{o/w}$ is fairly **easy to measure**
- $P_{o/w}$ often correlates well with many biological properties
- It can be predicted fairly accurately using computational models

---

**Lipophilicity** may be modelled using simple physical chemical models. The partition coefficient P is a measure of lipophilicity and is usually experimentally determined by equilibrating a sample of the compound in an octanol/aqueous buffer mixture.
The resulting emulsion is then separated.
Once separated, the concentration of the drug in each layer is measured and the partition coefficient is then calculated.

Carbon

# Hydrophobicity

حاسم

The hydrophobic character of a drug is crucial to how easily it crosses cell membranes and may also be important in receptor interactions.

- Changing substituents on a drug may well have significant effects on its Therefore, it is important to have a means of predicting
- this quantitatively.

---

معامل التجزئة

# Partition Coefficient [Log P]

- because biological membrane is mainly lipid in nature → solubilization of drug in the membrane is required for absorption

**Cell membrane:**

All cell contain a boundary called cell membrane, which encloses the cytoplasm.

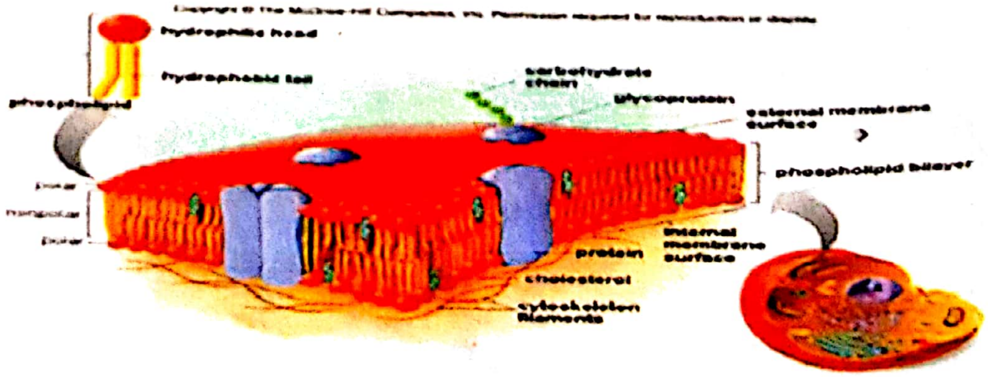
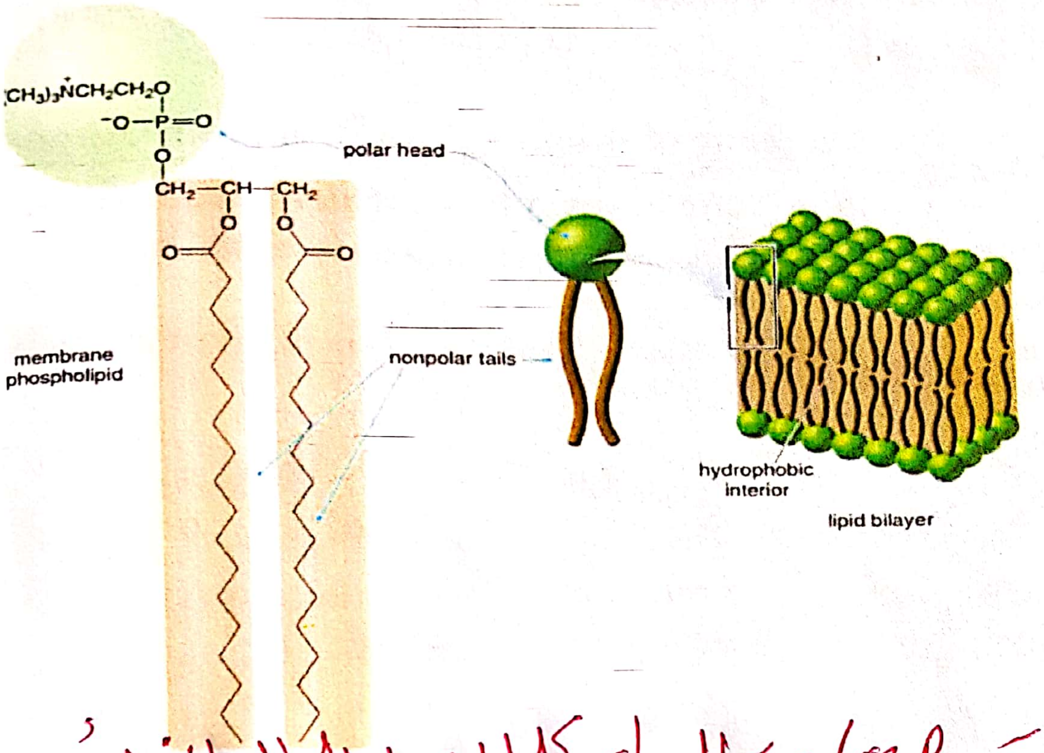

hydrophilic head
hydrophobic tail
phospholipid
carbohydrate chain
glycoprotein
external membrane surface
phospholipid bilayer
polar
nonpolar
polar
internal membrane surface
protein
cholesterol
cytoskeleton filaments

Figure: Cell membrane

كلما زودت acceptor و doner كلما قل Logp


(CH3)3NCH2CH2O
-O—P=O
O
CH2—CH—CH2
O O
O= =O
polar head
membrane phospholipid
nonpolar tails
hydrophobic interior
lipid bilayer

كلما زودت log P كلما المواد كلما يصل الى الدماغ أسرع .

## Partition Coefficient [Log P]

**xample;**

**nce different anaesthetics have similar log P° values,**
**he log P values of the gaseous anaesthetics ,**

**ther,=0.98**

**hloroform=1.97**

**and halothane= 2.3.**

**naesthetic activity increases from 0.98 to 2.3**

**Compounds having a log P value close to 2 should be capable of entering the central nervous system efficiently**

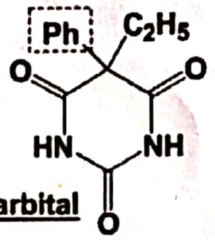
**his is generally found to be true. For example, the most potent arbiturates for sedative and hypnotic activity are found to have log P alues close to 2.**

# Partition Coefficient [Log P]

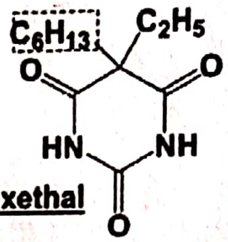
Log P = Log $\frac{\text{C o [conc of drug in organic phase n-octranol]}}{\text{Cw [conc of drug in aqueous phase water]}}$

- So one can modify a drug to improve its lipid solubility by introduction of hydrophobic gps

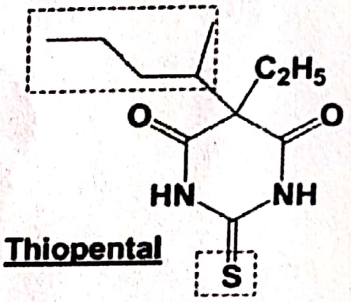
Where the hydrophobicity constants ($\pi$) of various chemical gps are available in tables so one can select the proper one


Ph
$C_2H_5$
O
O
HN
NH
O

**Phenobarbital**


$C_6H_{13}$
$C_2H_5$
O
O
HN
NH
O

**Hexethal**


$C_2H_5$
O
O
HN
NH
S

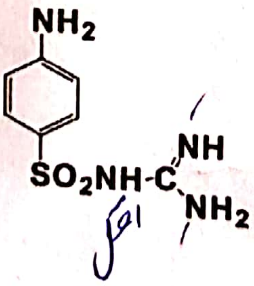
**Thiopental**

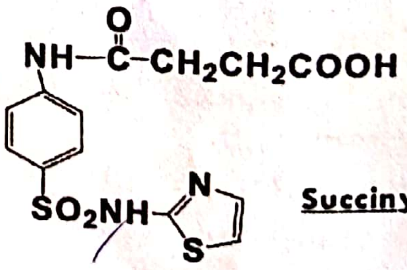
---

# Partition Coefficient [Log P]

•On the contrary, it may be useful to decrease the lipophilicity to prevent its absorption from GIT → localize its effect in GIT like intestinal sulfonamide [sulfaguanidine and succinyl sulfathiazole]

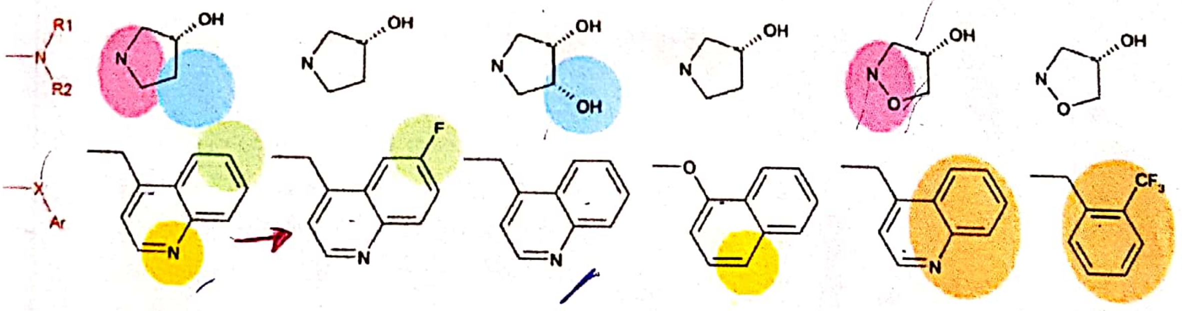
**Sulfaguanidine**


$NH_2$
$SO_2NH-C$
NH
$NH_2$


O
$NH-C-CH_2CH_2COOH$
$SO_2NH$
N
S

**Succinyl sulfathiazole**

# How can lipophilicity be altered?



logD 1.7 2.0 1.2 2.9 2.2 3.2

Here is a small series of compounds illustrating some techniques that are used to change the logD of a compound.

1. **Replacing hydrogen with a halogen** increases **the lipophilicity.**
2. Addition of **a hydroxyl group** decreases **the lipophilicity**. → because donor accep
3. Removal of the **quinoline nitrogen** to give a **carbocyclic** ring greatly increases the **lipophilicity**.
4. Addition of **an oxygen** into **the ring** adjacent to the **nitrogen** makes a more **lipophilic** compound.
5. Replacement of the **quinoline** with a **benzene** ring will make the compound **more lipophilic**, and this effect is enhanced by the addition of **a trifluoromethyl** group.

Original reference: *J. Med. Chem.*, 2007, *50*, 254.

## Molecular size

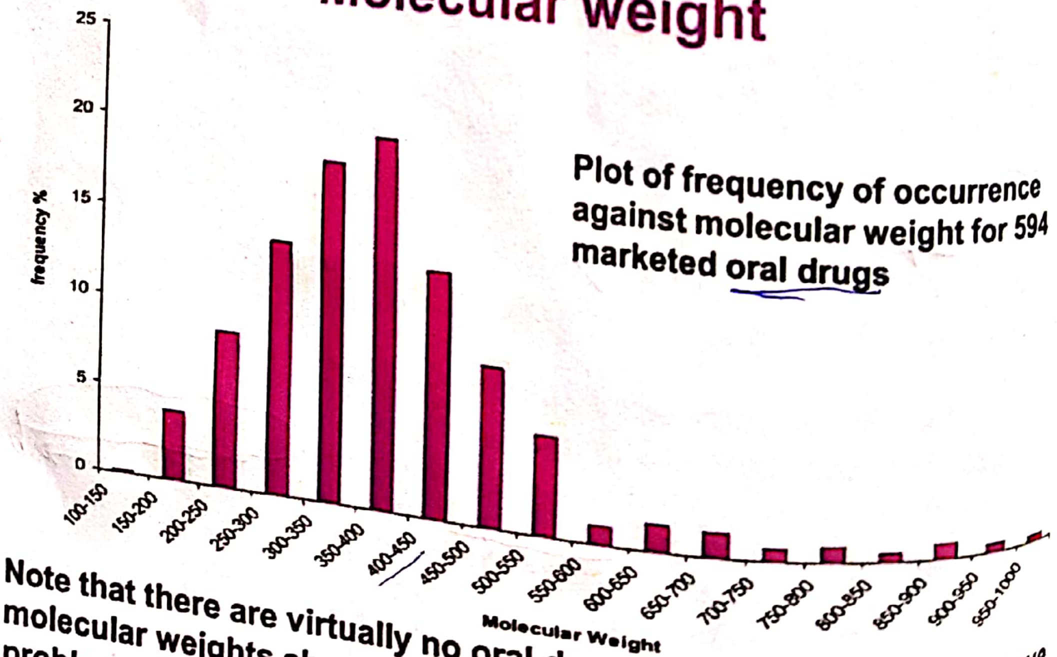
**Molecular size is one of the most important factors affecting biological activity, but it's also one of the most difficult to measure.**

**There are various ways of investigating the molecular size, including measurement of:**

- **Molecular weight (most important)**
- **Electron density**
- **Polar surface area**
- **Van der Waals surface**
- **Molar refractivity**

---

## Molecular weight



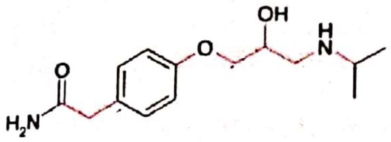
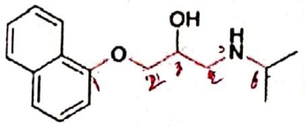
Plot of frequency of occurrence against molecular weight for 594 marketed oral drugs

**Note that there are virtually no oral drugs on the market which have molecular weights above 550. This is because they tend to suffer from problems like poor bioavailability – so when designing a new drug it's best to stick to molecular weights of under 500, and preferably nearer to 350-400.**

★ **Most oral drugs have molecular weight < 500**

## Number of rotatable bonds

A **rotatable bond** is defined as any single non-ring bond, attached to a non-terminal, non-hydrogen atom. Amide C-N bonds are not counted because of their high barrier to rotation.

| | | No. of rotatable bonds | Bioavailability |
|---|---|---|---|
|  | Atenolol | روابط 8 | 50% |
|  | Propranolol | روابط 6 | 90% |

The number of rotatable bonds influences, in particular, bioavailability and binding potency. Why should this be so?

---

## This seems like a lot to remember!

There are various guidelines to help, the most well-known of which is the **Lipinski Rule of Five**
The rules were used at Pfizer for a few years prior to their publication and since then have become widely used

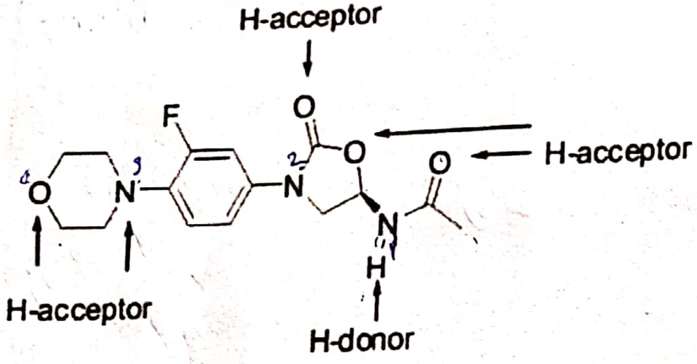
- molecular weight < 500
- logP < 5
- < 5 H-bond donors (sum of NH and OH)
- < 10 H-bond acceptors (sum of N and O)

An additional rule was proposed by **Veber**

- < 10 rotatable bonds

Otherwise absorption and bioavailability are likely to be poor. NB This is **for oral drugs only.**

*linezolid* (antibiotic)


H-acceptor
F
O
O
O
N
N
N
O
H
H-acceptor
H-acceptor
H-donor

$C_{15}H_{18}FN_3O_4$ (323.33)

***Lipinski's*** **rules of 5:**

- -logP < 5
- -molecular weight < 500 (600)
- -not more than 5 H-bond donors
- -not more than 10 H-bond acceptors (or 10 hetero atoms)
- -not more than 5 (10) rotatable bonds

**molecules which obey to Lipinski's rule of 5 have a high propensity for penetration into cells and for oral absorption**

---

# Drug-Receptor Interaction

## Medicinal Organic Chemistry
## and
## Drug Design

By

Ass Prof .Mokhtar Al-Ghorafi

# Drug-Receptor Interaction

**Drugs:** Compounds *reacting with biological systems* producing *biological response.*

**Receptors**: Protein molecules found on rigid or semi-rigid biologically important macromolecules as:

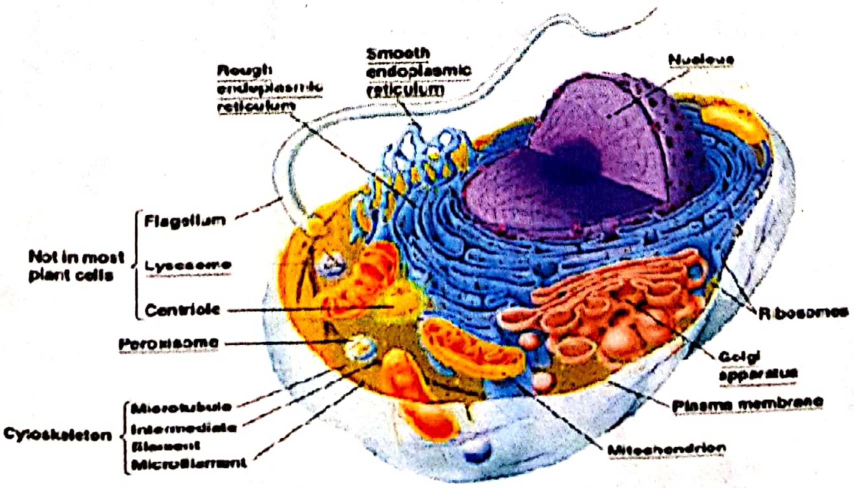
بروتين موجود على cell membrane

**1.Nucleic acids [DNA, RNA].**
**2.Enzymes [Acetyl choline esterase, MAO, ACE....].**
**3.Cell membrane**

## Drug target

Since life is made up of cells, then quite clearly drugs must act on cell.

**Cell structure :**


Rough endoplasmic reticulum
Smooth endoplasmic reticulum
Nucleus
Flagellum
Not in most plant cells
Lysosome
Centriole
Peroxisome
Ribosomes
Golgi apparatus
Plasma membrane
Cytoskeleton
Microtubule
Intermediate filament
Microfilament
Mitochondrion

# Drug target

**Cell membrane:**

All cell contain a boundary called cell membrane, which encloses the cytoplasm.

passive الدواء يؤ

like dissolve like

يسمى الـ active

لازم يشيل حاجة زي الـ

[illegible] بالطاقة

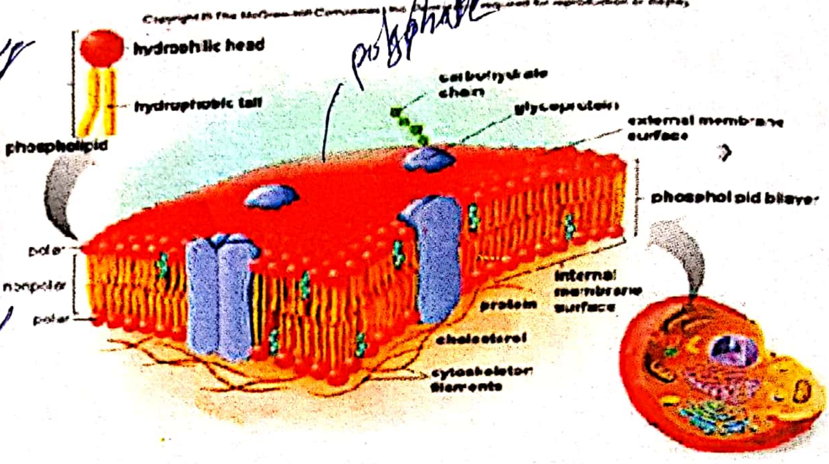

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
hydrophilic head
hydrophobic tail
phospholipid
polyphate
carbohydrate chain
glycoprotein
external membrane surface
phospholipid bilayer
polar
nonpolar
polar
internal membrane surface
protein
cholesterol
cytoskeleton filaments

Figure: Cell membrane

أمشيش حاجة مع المياه

الكورتيزونات

(دكسا + تاكوسيل)

الكورتيزون بتدخل في DNA

# Drug target at the molecular level

**Receptors:**

Receptors are macromolecular lipoprotein, present in the cell membrane or within the cell, with which drugs bind reversibly or irreversibly in order to produce an pharmacological effect.

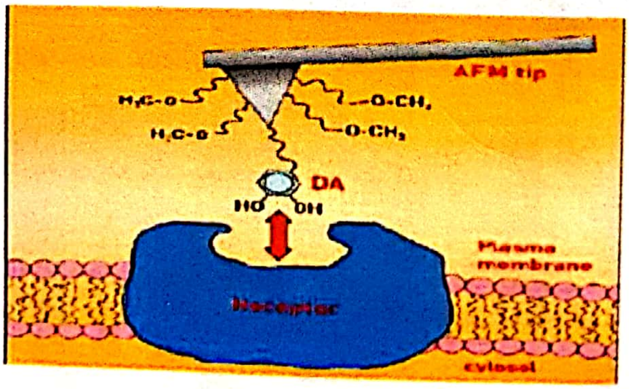
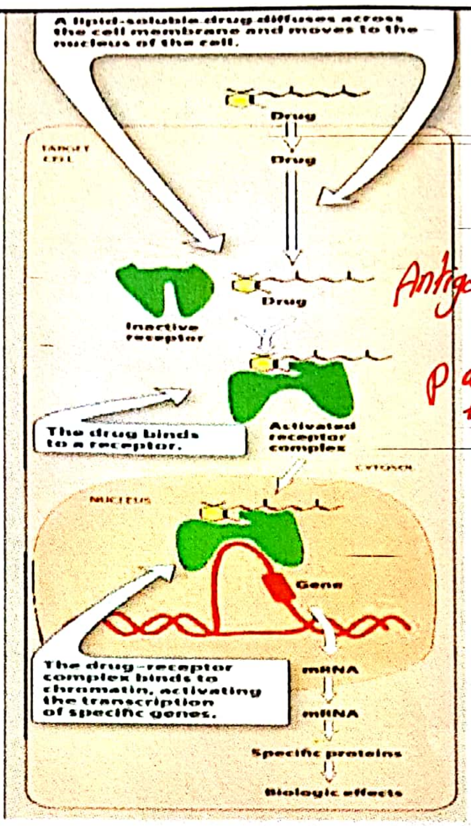

AFM tip
$H_3C$-O
O-$CH_3$
$H_3C$-O
O-$CH_3$
DA
HO
OH
Plasma membrane
Receptor
cytosol

Figure: Receptor


A lipid-soluble drug diffuses across the cell membrane and moves to the nucleus of the cell.
Drug
TARGET CELL
Drug
Drug
Inactive receptor
The drug binds to a receptor.
Activated receptor complex
CYTOSOL
NUCLEUS
Gene
The drug-receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Biologic effects

Antagonist 70 %

Partial Agonist ← 80% → partial agonist

potancy → هي فعالية الدواء بأقل جرعة

الصفحة ٧

→ ability of drug to change The form of receptor

## Some important terms

drugs receptor complex.

1. **Affinity:** the ability of the drug [D] to interact with the receptor [R] forming D-R complex.

هي قدرة الدواء على تغيير شكل المستقبل

2. **Intrinsic activity:** a measure for the ability of the D-R complex to produce biological effect.

3. **Agonist:** a drug with **both** affinity & intrinsic activity.

4. **Partial agonist:** a drug with **good affinity** but **moderate** intrinsic activity.

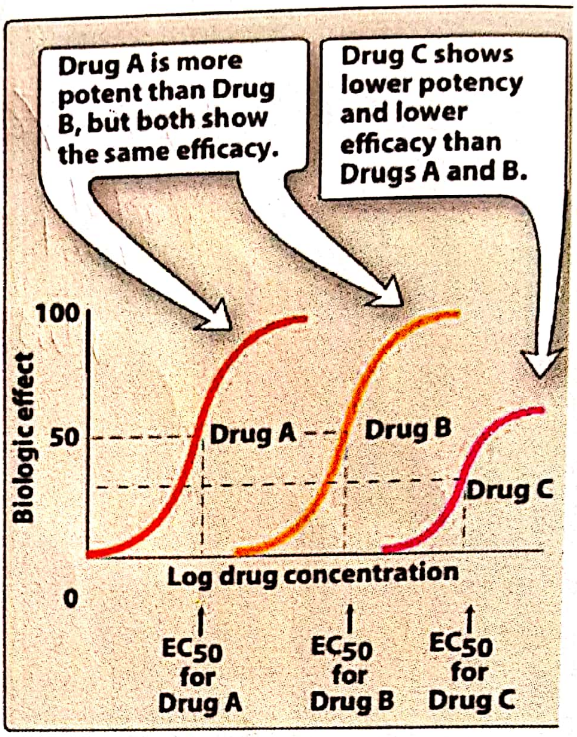
5. **Antagonist:** a drug with **affinity** for a receptor but with **no** intrinsic activity.

← إذا الدواء صنع الطبيعي ومفيش

← إذا الدواء دخل يحجز ومفيش ← Antagonist

← إذا الدواء دخل وغير الشكل ← Agonist

اذا تركيز الدواء اقل يختلف ال activity كلها.



الدواء نوعين

## Drug Receptor Interactions

يرتبط في المستقبل وهذا نسبة ٩٠ ال٩٥٪ من الأدوية.

| Structurally Specific Drugs [SSD] | Structurally Non Specific Drugs [SNSD] |
|---|---|
| - Drugs producing their effects by *interaction with specific receptors.*<br>- Their activity depends on *3D chemical structure of the drug which should adapt to the 3D structure of the receptor.* | - Drugs producing their *effects by physical phenomenon with no interaction with specific receptors.*<br>- **E.g. Antacids,① Adsorbents.②** |

الدواء الذي يحصل له امتصاص مركزي يسمى specific

لا يحتاج الى مستقبل
③ فوارت اليوركول
④ المسكنوت [illegible] الاستاخ
٤ ppi

# Drug Receptor Interactions

**Forces binding SSD to receptors are either**

**[i] Irreversible drug-receptor interaction**

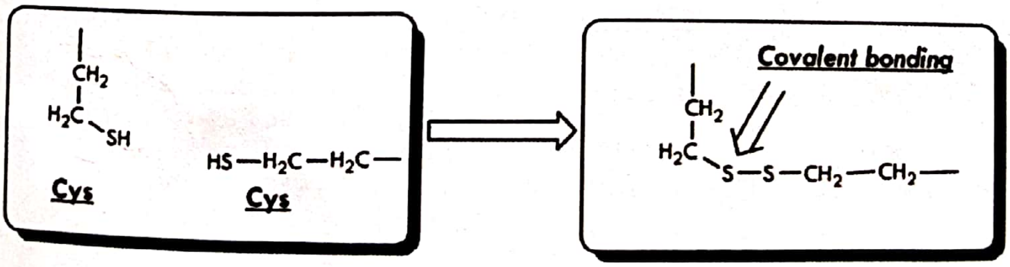
**[ii] Reversible drug-receptor interaction**

**Covalent bonds:**

- The ***strongest bonding force*** [250 Kj / mol].
  - Preferred ***if long lasting irreversible effects are desired***. E.g ***Anti-bacterial & Anti-cancer drugs.***
  - ***The drug effect is terminated through:***
    - Catalytic cleavage of D-R linkage [by enzymes or acid-base catalysis].
    - Metabolic turnover of receptor molecules.

# Drug Receptor Interactions

- E.g. ***Mechlorethamine*** [alkylating agent], through its Aziridinium moiety → form covalent bond with SH, COO - or $PO_4$ anions of proteins or nucleic acids → prevent their normal participation in cell division.



# Drug Receptor Interactions

## Drug target at the molecular level

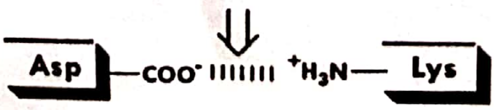
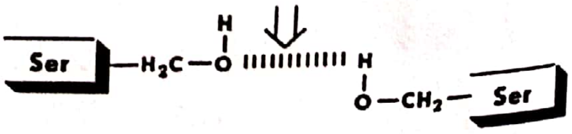
Drugs bind to the receptors by **inter molecular bonds**. Every drug contain some specific functional group or binding group and receptors have binding site. Interaction is caused by binding site and binding group by following bonds:

1. Electrostatic or ionic bond
2. Hydrogen bond
3. Van der walls interactions
4. Dipole – dipole and ion- dipole interaction
5. Repulsive interaction

---

# Drug Receptor Interactions

## ii] Reversible D-R interactions

| 1. Ionic bonds | 2. Hydrogen bonds |
|---|---|
| • **Strong electrostatic bonding force** between groups having **opposite charges.**<br>• Most drugs are **weak acids or weak bases**, when **ionized in water →** react with the **opposite charge on the receptor**:<br>* Cationic → e.g. **NH2 gp of** amino acids.<br>* Anionic → e.g. terminal **COOH gp of** amino acids.<br> | • Formed between **electro-negative atoms as O,N,Cl.... & protons attached to electro-negative atoms.**<br>• **Hydrogen bonds easily brocken** → **dissociation of D-R complex.**<br>• It's formed between H-donor & H-acceptor:<br>✓ CH3 group → **not donor not** acceptor.<br>✓ OCH3, F → H-acceptor.<br>✓ OH, NH2 → H-donor & H-acceptor.<br> |

# Drug Receptor Interactions

## Intermolecular bonds

### 2. Hydrogen bond :

Hydrogen bond takes place between an electronic rich hetero atom and electron defficient hydrogen. electronic rich hetero atoms has to haven a lone pair of electron. Usually nitrogen or oxygen atom.

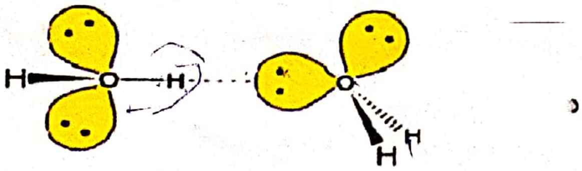


Figure: Hydrogen bond

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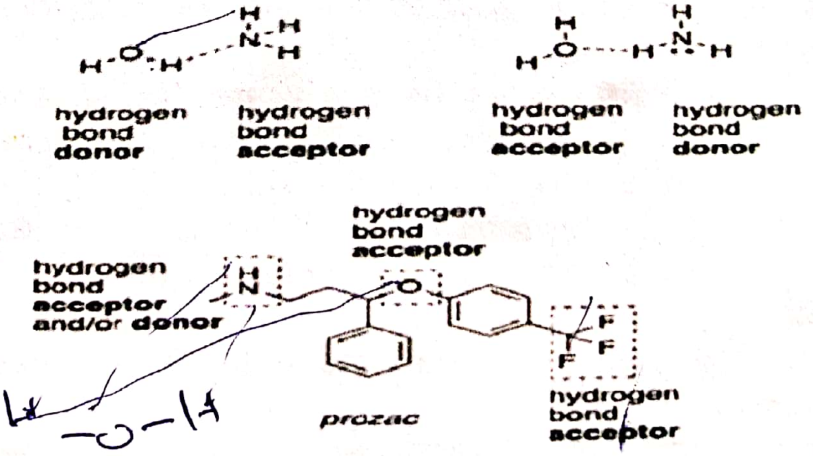
# Drug Receptor Interactions

## Intermolecular bonds

### 2. Hydrogen bond :


H
O
H
H
N
H
H
hydrogen bond donor
hydrogen bond acceptor
H
O
H
H
N
H
H
hydrogen bond acceptor
hydrogen bond donor
hydrogen bond acceptor
hydrogen bond acceptor and/or donor
H
N
O
F
F
F
prozac
hydrogen bond acceptor

H —O—H

Figure: Hydrogen bond

HO — I

$H_2O$

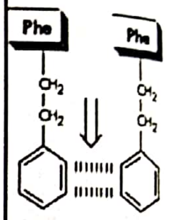
أضعف روابط لكنها أكثر الروابط في الجسم لأن الجسم كله Non-polar.

Non-polar with Non-polar.

## Drug Receptor Interactions

### (أضعف الروابط 3. Van der Waal's interactions (VdW)

- 1.9 Kj / mol.
- **Between hydrophobic molecules** [either aromatic or aliphatic].
- It's due to **differences in electron density in these neutral, non-polar molecules** → a **transient area of ↑ e-density & another area of ↓ e-density → the area of ↑ e-density on one molecule attracts another hydrophobic** area of ↓ **e-density on another molecule.**



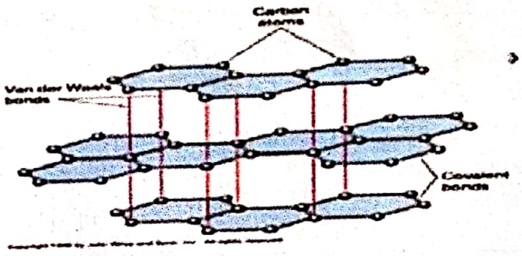


Figure: van der waals interaction

فائدة ← كونه الدوا Lipophilic يكسب

① high absorption
② high destribution * غلط
③ ~~high~~ ③ Less metabolism
④ Less excretion
⑤ high half life
⑥ less dose

## Drug Receptor Interactions

### Hydrophobic/Lipophilic interactions.

hydrophobic bonds are formed between **non-polar hydrocarbon groups on the drug and those in the receptor site.**

These bonds are **not very specific** but the **interactions do occur** to exclude water molecules.

**Most of the drug molecules** have a **non-polar portion** (alkyl or aryl groups) which **may combine with non-polar portion** of the receptor site **through hydrophobic forces.**

**Hydrophobic interactions** are generally **weak**, but **important.**

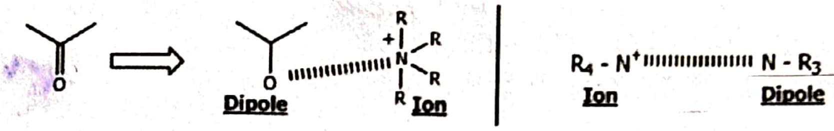
Hydrophobic interactions are probably significant **in driving interactions**

(a) **Between lipophilic drugs** and the **lipid component of biological membranes**

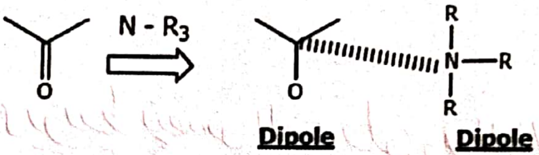
(b) **Between drugs and relatively nonpolar** (non charged) **receptor region**

## 4. Ion dipole & Dipole-dipole interactions

- **Ion-Dipole interaction**: an electrostatic attraction between a full charge [ion] and a partial charge [dipole]. E.g. :


Dipole
Ion
$R_4 - N^+$
$N - R_3$
Ion
Dipole

- **Dipole –Dipole interaction:** an electrostatic attraction between partial opposite charges. E.g. :


N - R3
Dipole
Dipole

## Drug Receptor Interactions

### Intermolecular bonds

**4. Dipole dipole interaction:**

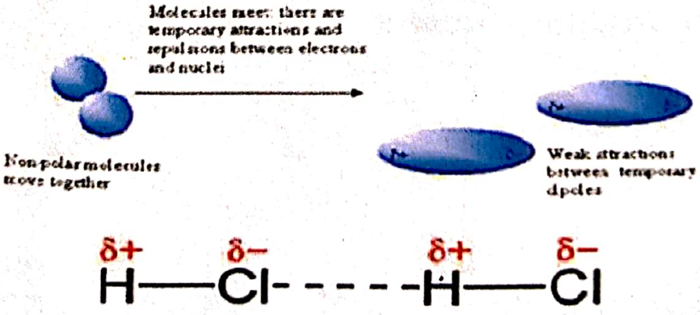
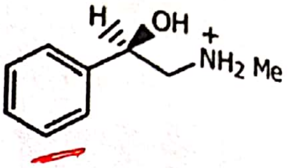

Molecules meet: there are temporary attractions and repulsions between electrons and nuclei
Non-polar molecules move together
Weak attractions between temporary dipoles
δ+ δ− δ+ δ−
H—Cl- - - - -H—Cl

Figure: dipole dipole interaction

## A Hypothetical Neurotransmitter is composed of:



1. **Aromatic ring** [Van der Waal's force].
2. **Alcoholic group** [hydrogen bond].
3. **Cationic center = +ve nitrogen center** [ionic bond].

مستقبل افتراضي

العالم

## Beckette's Hypothesis of receptor
## [Binding Hypothetical Neurotransmitter]

***Receptor is made of 3 complimentary binding regions:***

- **Flat area**: to bind to aromatic ring [Van der Waal's interaction].
- **Anionic site**: to bind cationic nitrogen [ionic bond].
- **Cavity**: for fitting **connecting chain between aromatic ring & cationic sit**

هي المسافة ما بين
الحلقة الار
والموجب

لما كان الدواء يرتبط بنفس الذي خلق رب العالمين ← agonist

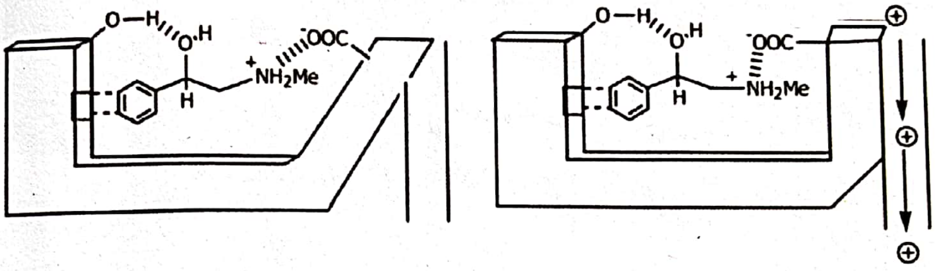
ولما كان الدواء يرتبط أكثر مما يرتبط الطبيعي لا يستطيع الطبيعي الإزاحة من مكان

## How does a receptor change its shape?

**Bonding forces between drug & receptor must be *large enough* to change the shape of receptor**

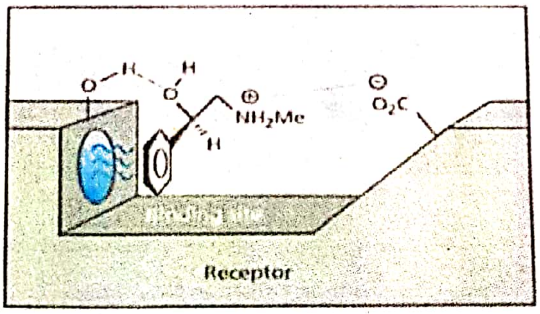
- Hypothetical receptor may be a part of an ion channel that is closed when neurotransmitter is absent.

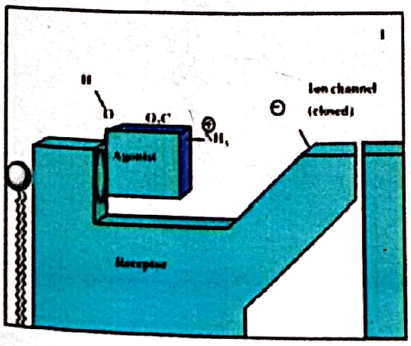
- When drug bind hypothetical receptor → receptor alters its shape to obtain the best binding interaction [**conformational changes**].
- COO- group of the receptor is pulled closer to +ve nitrogen of the messenger → **opening of lock-gate**.
- Gate remains open till the messenger detaches from the binding site.
- Finally, the receptor returns to its original shape.

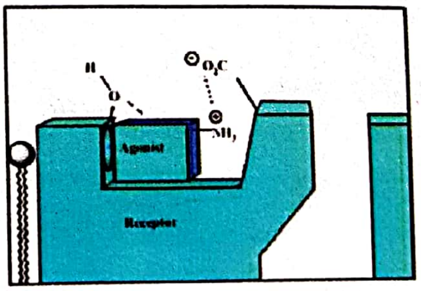

O—H
O·H
H
NH₂Me
OOC
+
⊕

عندما أكبرا للدواء
أكبر ال size يا طول يا عرض.

## How does the binding site change shape?


O
H
NH₂Me
O₂C
Binding site
Receptor


Ion channel (closed)
Agonist
Receptor
O₂C
NH₃


O₂C
NH₃
Agonist
Receptor

- Induced fit alters protein shape
- Opens ion channel

إذا أردت أن تصمم دواء Agonist يجب ان

## Design of Agonists

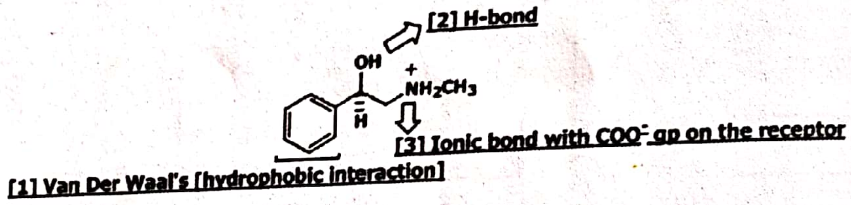
**The drug must have:**

- The correct binding groups.
- The correct orientation of the binding groups. chiral
- The right size & shape for the binding site. الحجم والشكل

اذا كان الـH الى الداخل امام لازم يكون امام واذا كان خلف لازم يكون خلف

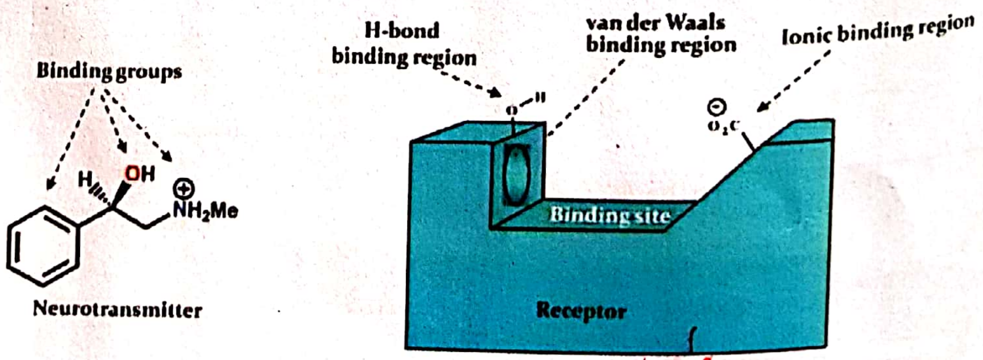
### Correct binding groups

1. **In the hypothetical neurotransmitter:**


[2] H-bond
OH
+
$NH_2CH_3$
H
[3] Ionic bond with $COO^-$ gp on the receptor
[1] Van Der Waal's [hydrophobic interaction]

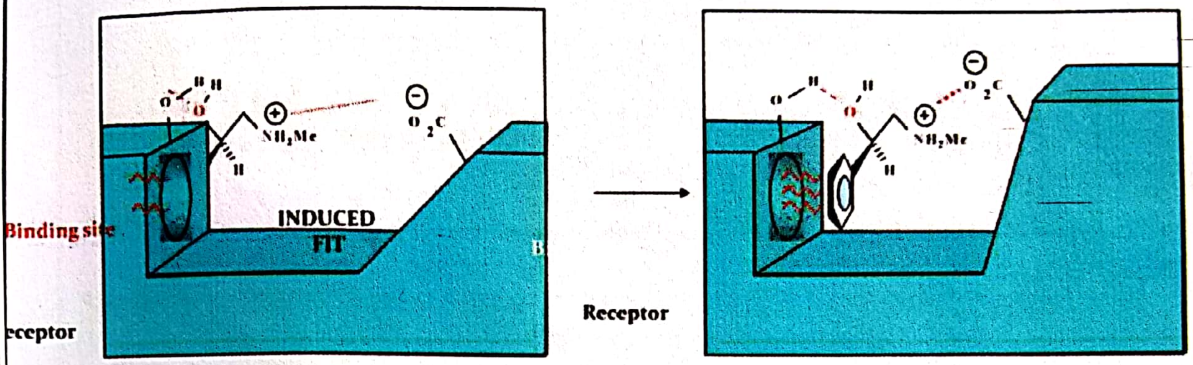
الدهنية مرآة رح

## Design of a agonist and receptor


Binding groups
H
OH
NH₂Me
Neurotransmitter
H-bond binding region
van der Waals binding region
Ionic binding region
O–H
O₂C
Binding site
Receptor

محل الارتباط

# Design of an agonist and receptor

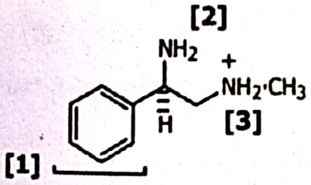

Binding site
eceptor
H
H
O
O
NH₂Me
O₂C
H
INDUCED FIT
Receptor
H
O
H
O
NH₂Me
O₂C
H

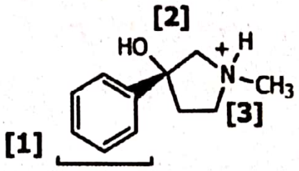
بعد الالتصاق

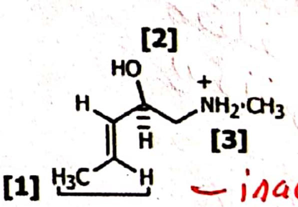
Induced fit allows stronger binding interactions

---

## 1.Possible agonists are :


[2]
NH2
+
NH2·CH3
H
[3]
[1]


[2]
HO
+
H
N
CH3
[3]
[1]


[2]
HO
+
H
NH2·CH3
H
[3]
[1]
H3C
H

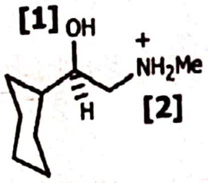
– inactive

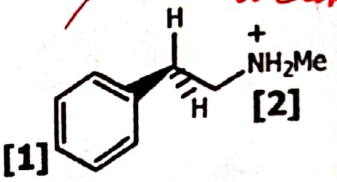
| | | |
|---|---|---|
| contains amino group instead of OH, which is capable of forming H-bond. | Contain an extra bridge of two carbons, so, all binding groups are present. | Contain a flat hydrophobic double bond instead of benzene binding receptor by Van der Waal's forces. |

## 1.While the following possesses two interactions only [not agonists]:

Inactive No ⑥

inactive because No OH weak (✓)


[1] OH
+
NH₂Me
H
[2]



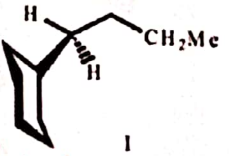
| Contain Cyclohexane instead of benzene [not planner] → drug can't bind the the flat area of the receptor. | Removal of OH group → drug can't form H-bonding. |
|---|---|

## Design of an agonist

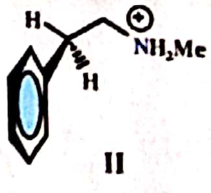
لما يجي يرتبط بشكله مختلف وبالتالي ما راح يدي نفس المفعول،

ايضا لانه مافيش OH

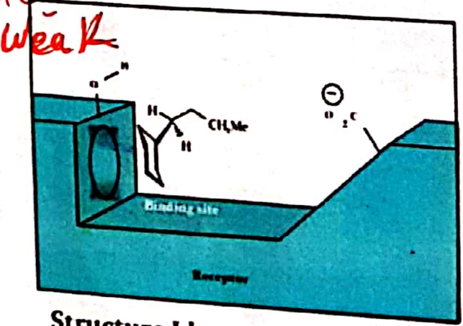
Weak



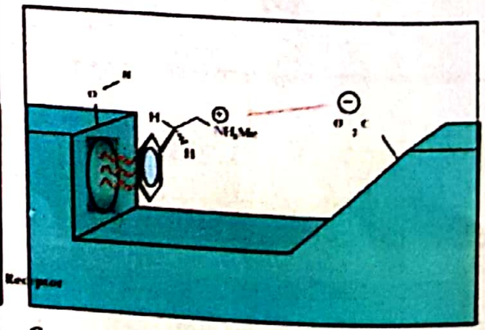
I



II


O
H
H
CH₂Me
H
⊖
O₂C
Binding site
Receptor

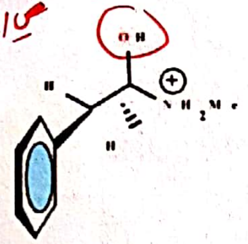
Structure I has one weak binding group - negligible activity


O
H
H
⊕
NH₂Me
H
⊖
O₂C
Receptor

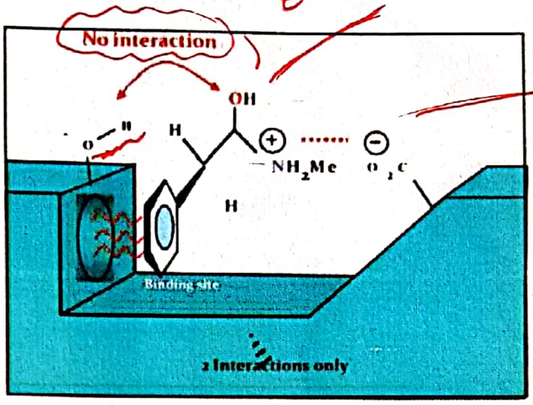
Structure II has 2 of the 3 required binding groups - weak activity

## Design of an agonist

بعيدة لا تتطابق مع المستقبل



بعيدة عن الموقع


No interaction
OH
O
H
H
NH2Me
O2C
H
Binding site
2 Interactions only

inactive

غير نشط بسبب
على الرغم من وجود OH
في المركب الا انها بعيدة
عن الموقع.
مادام و OH
مغيرة من مكانها
فالدوا inactives

- Binding groups must be positioned such that they can interact with complementary binding regions at the same time
- Example has three binding groups, but only two can bind simultaneously
- Example will have poor activity

الموقع

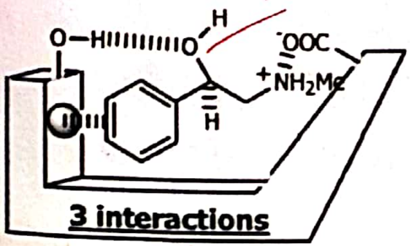
## 2. Position of the binding groups

The compound may have correct binding groups but NOT in right position.

Optical isomers of the hypothetical neurotransmitter has only two binding forces → ***weaker binding → no activity.***

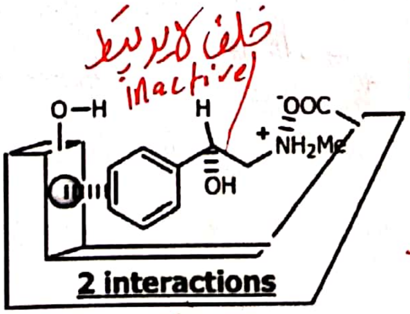
***N.B:*** *optical isomer of a pure agonist isn't necessarily a pure antagonist.*

امام راح يرتبط


O—H
H
O
-OOC
+NH2Me
H
3 interactions

امام

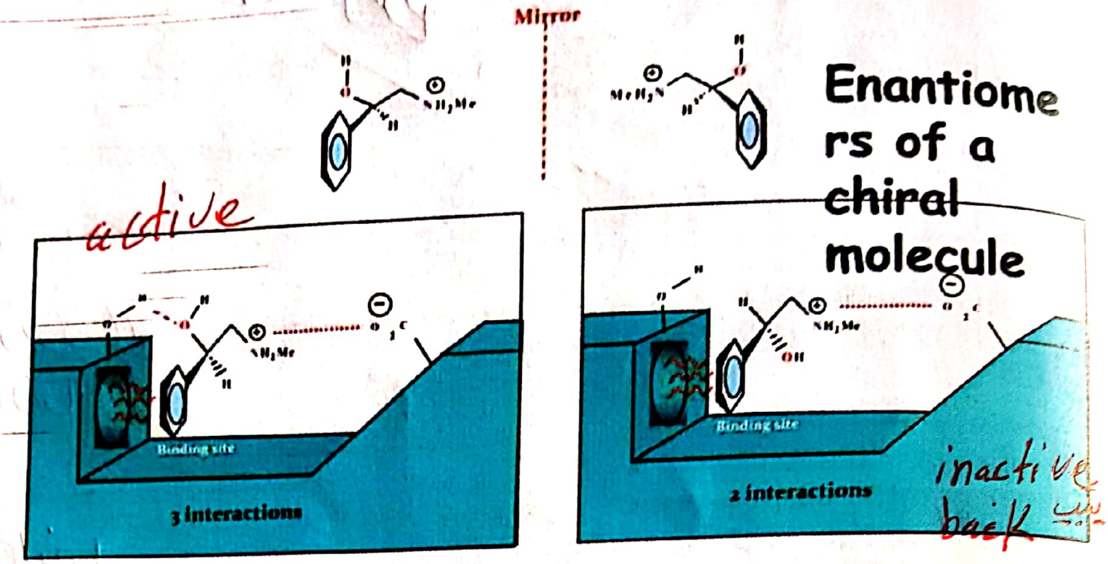
خلف لا يرتبط
inactive


O—H
H
-OOC
+NH2Me
OH
2 interactions

خلف

لذا جاء الايزومر امام
راح يرتبط بال OH
و اذا جاء خلف لا يرتبط
back

# Design of an agonist



Mirror
active
Binding site
3 interactions
Binding site
2 interactions
inactive
back

**Enantiomers of a chiral molecule**

- One enantiomer of a chiral drug normally binds more effectively than the other
- Different enantiomers likely to have different biological properties

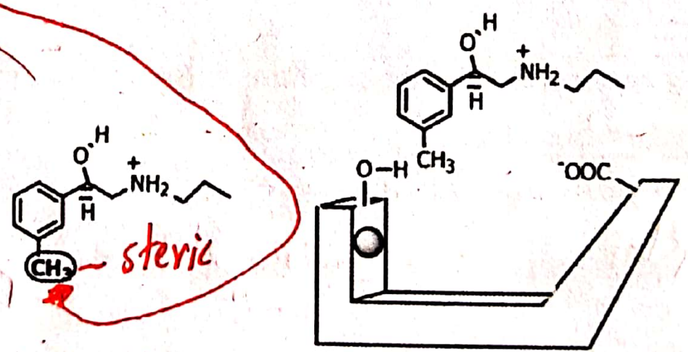
---

### 3. Size & shape of the drug

أتنبه لعصم تدلع
المثكل تضيف له CH3
اللي يكون عرض
إما كذا لا

It's possible for a drug to have correct binding groups in correct positions BUT *failed to interact as it has wrong shape or size.*

**e.g.**



O
H
NH2
H
CH3
steric
O
H
NH2
H
CH3
O–H
⁻OOC

التطابق مع
الدواء يكون
أقل وبالتالي يصبح
inactive

**p. methyl group** → prevent structure from sinking deep enough for effective binding.

**Long alkyl chain on N** → makes the part of the molecule too long for space available to it.

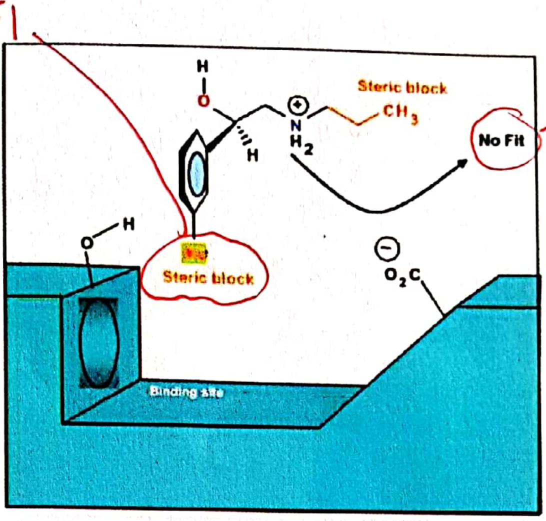
كذلك لا تكبير الدواء زيادة التكبير له حدود مثلاً تقوم بعمل
branch طويل وكبير الدواء بعد ذلك ما راح يتطبق.

~~انتبهي ان كونوا~~ أتمنى ان تكونوي أيامكم القادمة Agonsit وليس antigonist
كونوا antigonist للآخرين لما يكون فيه الم pain

## Design of an agonist

إعاقة فراغية تخلي الدواء يخرج

Not fit
غير مناسب
لا يطابق .



- Agonist must have correct size and shape to fit binding site
- Groups preventing access are called steric shields or steric blocks

التكبيرة قواعد أما طول أو عرض
• عندما الدواء يكون Antagonist لازم يكون ارتباطه أعلى من الطبيعي .

## Design of Antagonists

### 1.Competitive Antagonist [acting at the binding site]

يتنافس مع الطبيعي

① Antagonist compete with the normal agonist [*structurally similar to normal substrate*].

بشكل كبير — في موقع الارتباط

② Antagonist fits firmly [perfect fit] to the binding sites of the receptor → no change in the shape of the receptor → NO biological effect.

لكن ما يعملوش تشكيل المستقبل

Antagonist يرتبط أعلى من الطبيعي لأنه أكبر

③ Antagonist must *bind more strongly* to receptor [higher affinity].

**PERFECT FIT** means → when the size of the drug = the size of the active site of the receptor → no change in shape.

إذا الشركة صنعت دواء بنفس الشكل المستقبل بنفس الحالة التحدث تغيير الشكل القفل هذا حق المستقبل

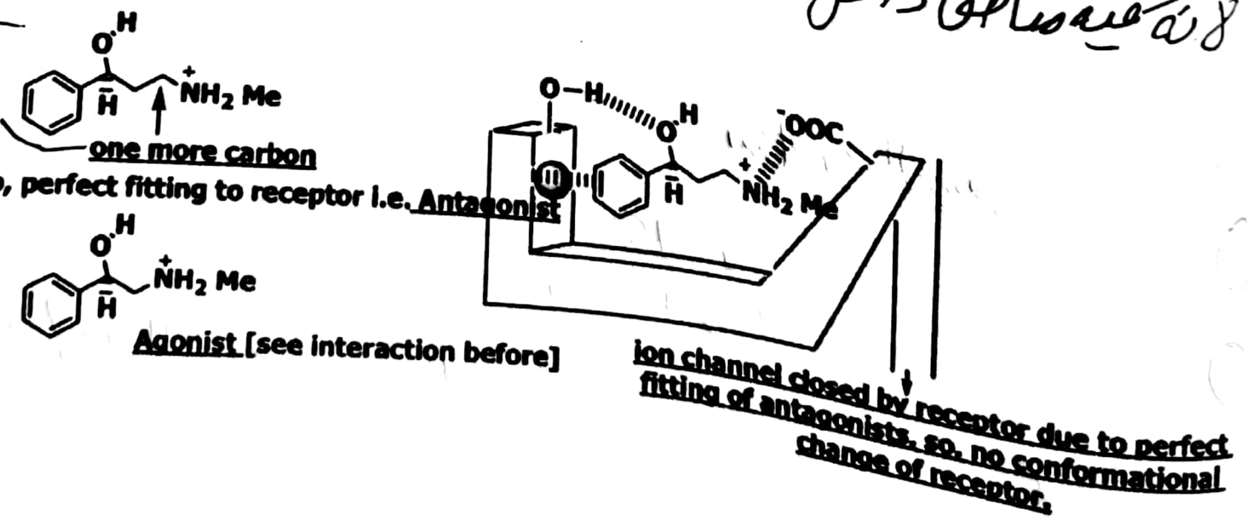
There are several strategies in designing antagonists, but one way is to design a drug which is the right shape to bind to the receptor binding site,

The compound shown in Fig. fits the binding site perfectly and, as a result, does not cause any change of shape. Therefore, there is no biological effect and the binding site is blocked to the natural neurotransmitter.

← كلما كان large binding كلما كان الارتباط أعلى وأكثر
high

ليس شرط لو تعمل تطويل لطول ممكن تعمل بالعرض
لأنه فيه مناطق داخل المستقبل فاضية. مثلا أعمل لها حلقة بأتخلي ارتباطها أعلى

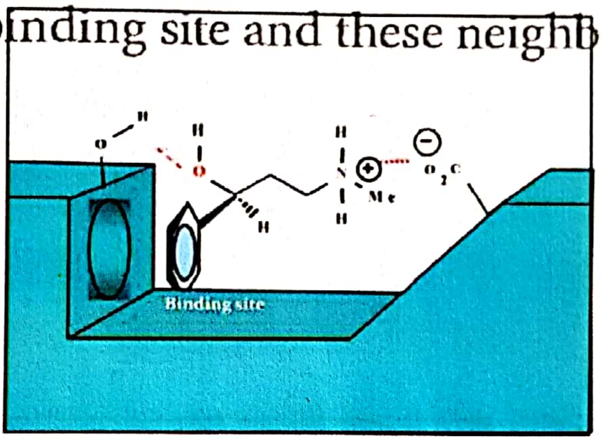
زاوية كربونية
السلاسل للدوار
لم تتغير الشكل



O H
NH₂ Me
H
one more carbon
so, perfect fitting to receptor i.e. Antagonist
O H
NH₂ Me
H
Agonist [see interaction before]
O—H
O H
⁻OOC
NH₂ Me
H
ion channel closed by receptor due to perfect fitting of antagonists, so, no conformational change of receptor.

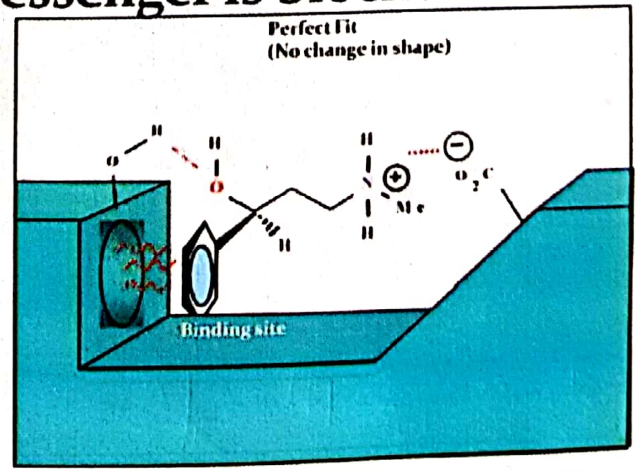
Another strategy is to find different binding regions within the binding site that are not used by the natural chemical messenger.

It is quite common to find antagonists that are larger than the natural messenger and which access extra binding regions beyond the reach of the usual messenger. Many antagonists are capable of binding to both the normal binding site and these neighbouring regions.


O
H
H
O
H
N
Me
H
O2C
H
Binding site

## Design of antagonists

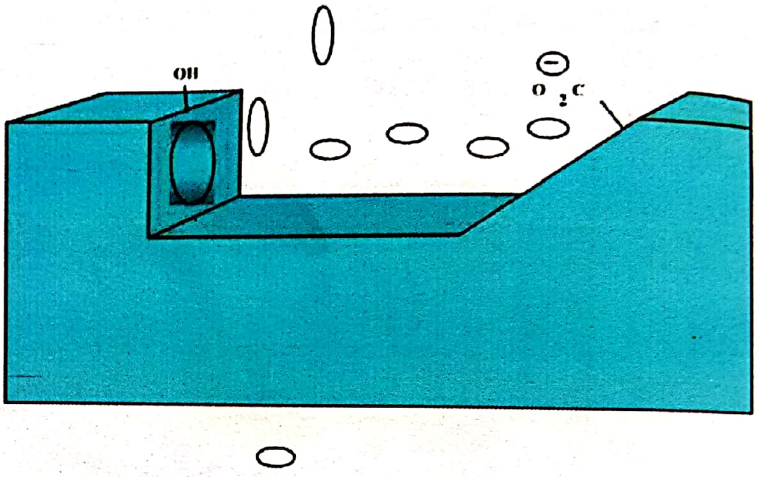
- **Antagonists bind to the binding site but fail to produce the correct induced fit - receptor is not activated**
- **Normal messenger is blocked from binding**


Perfect Fit
(No change in shape)
O
H
H
O
H
N
Me
H
O2C
H
Binding site

شرط ان تحمل تطويل الطول ممكن تعمل بالعرض
ليس لازم فيه مجموعة داخل المستقبل فاضية مثلا ممكن نعمل حلقة بالتكافؤ الارتباط
أعلى

# Design of antagonists

Drugs could be designed to interact with some of these extra binding regions, such that the resultant binding produces a quite different induced fit from that obtained when the natural messenger binds an induced fit that fails to activate the receptor.


OH
O₂C
Receptor binding site
Extra binding regions

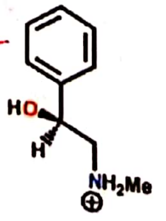
---

# Design of antagonists

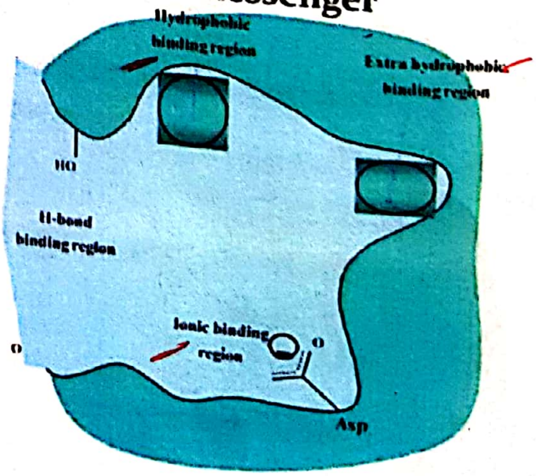
The three important binding regions are still present, but our 'map' shows an extra hydrophobic region which could act as a potential binding region.

Antagonists can form binding interactions with extra binding regions neighboring the binding site for the natural messenger

هذا الدواء الذي حلقة رب العالمين

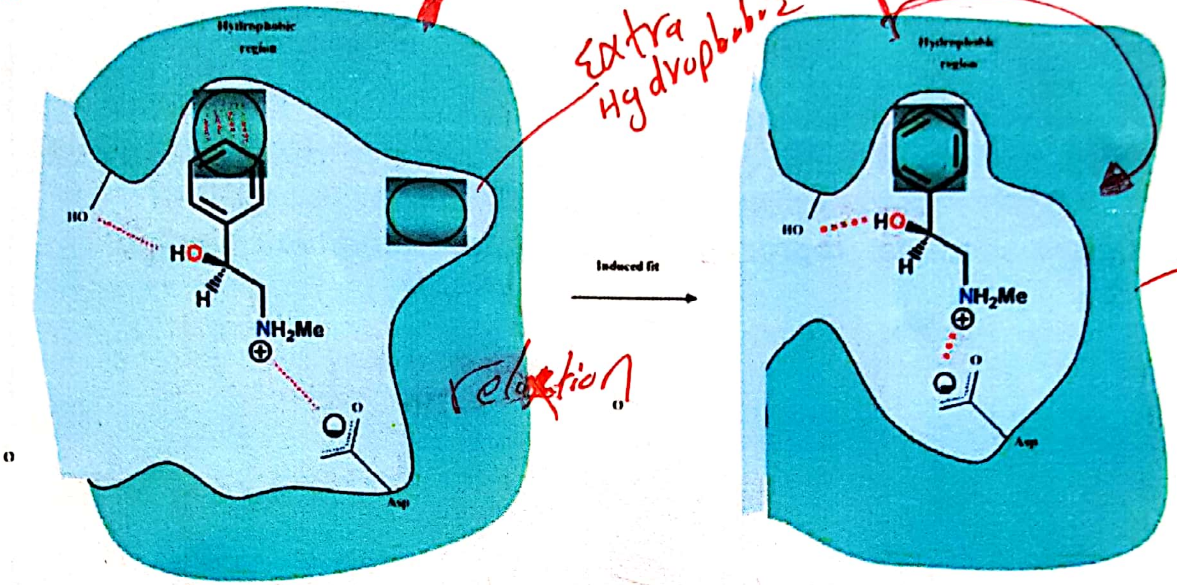


Hypothetical neurotransmitter


Hydrophobic binding region
Extra hydrophobic binding region
HO
H-bond binding region
Ionic binding region
O
O
Asp

**Now design a molecule which would bind to all four of these binding regions . This molecule will bind more strongly than the natural messenger due to the extra binding interaction**

ماذا يحصل للمستقبل عندما ارتبط بالدواء هل تغير او ماتغيرش ؟
تغير مثلاً قد يتغير الى contriction أو relaxation على حسب نوع المستقبل


Hydrophobic region
HO
HO
H
NH2Me
Asp
Induced fit
Hydrophobic region
HO
HO
H
NH2Me
Asp

Extra Hydrophobic

relaxation

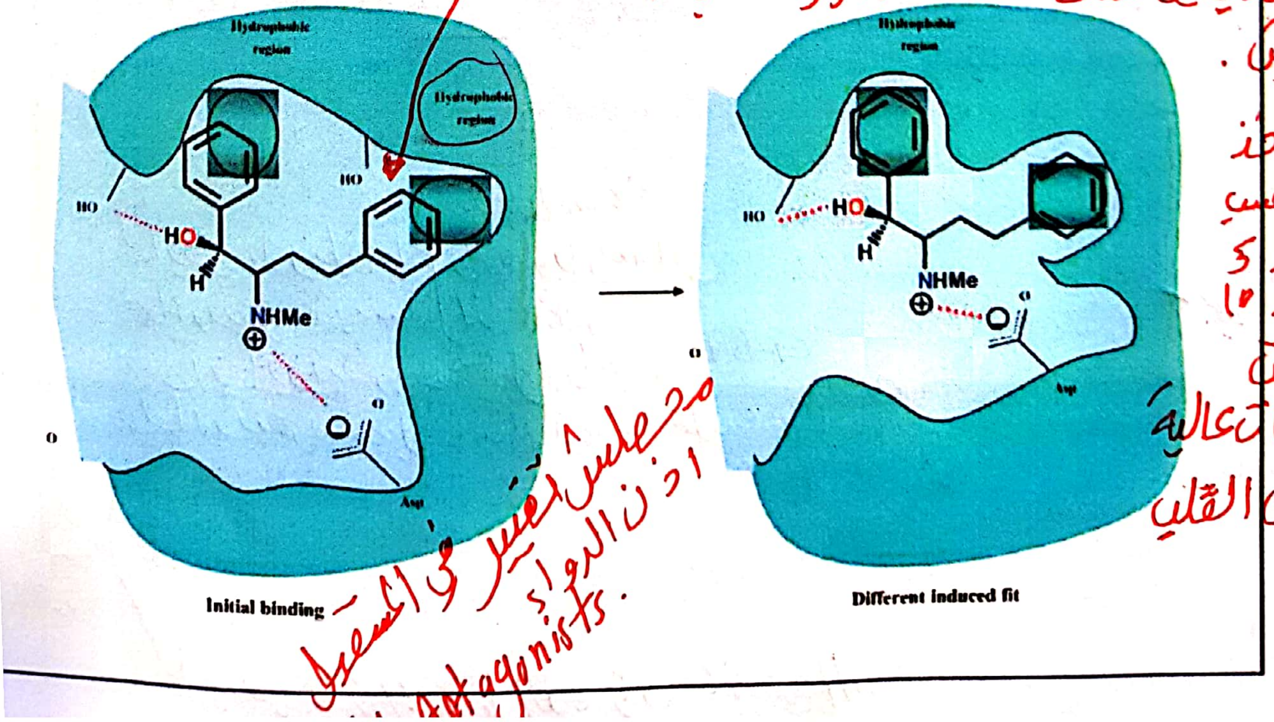
cont

## Design of antagonists

الدواء بواسطة حلقة
يستطيع المستقبل ان يغير من شكله ؟
يحاول حاول لكن مقدرش

## Different induced fit resulting from extra binding interaction

يستطيع الكيميائي ان يدخل لا
يستطيع الادينالين اذ يرفع لك الضغط او ضربات القلب ؟
ندرش .
حد يأخذ
على حسب
ة ايو ٥
٤ أيو ١٠
ا قلق
جرعات عالية
يوقف القلب


Hydrophobic region
Hydrophobic region
HO
HO
HO
H
NHMe
Asp
Hydrophobic region
HO
HO
H
NHMe
Asp

Initial binding

Different induced fit

محصلش التغير في المستقبل لان الدواء antagonists.

الدفعة ٤٤ صيدلة الدكتور مختار فتحي مصلح - المحاضرة الثالثة.

علم الدواء الجزيئي - الدكتور مختار [illegible]

If we know **the shape and make-up** of a **receptor binding site**, then we should be able to design drugs to act as agonists or antagonists.

**In the past the theoretical** shape of many **receptor** sites was hypothesized by synthesizing a **large number of compounds** and identifying those molecules that fitted

**Nowadays,** the use of genetic engineering, **X-ray crystallography of protein targets, and computer-based molecular modelling** allows a more accurate representation of proteins and their binding sites

فيه أدوية لا ترتبط بالمستقبل بشكل Direct وانما ترتبط Allosteric.

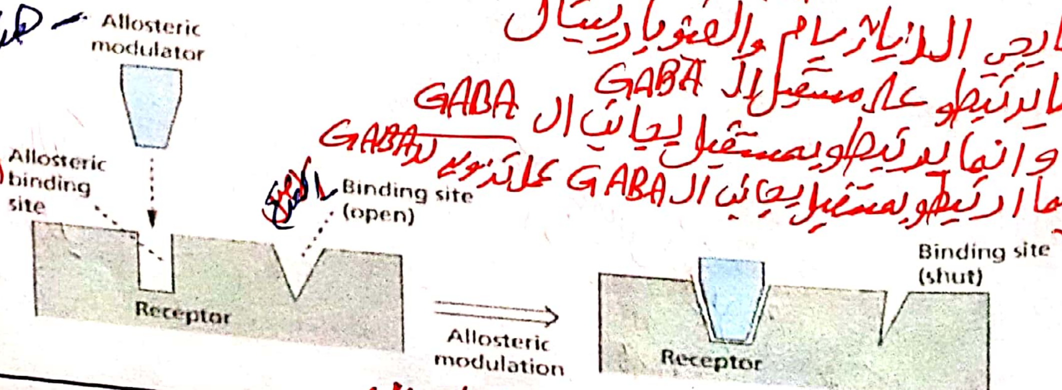
الديازيبام لا يشتغل على ال GABA وانما يآزروها.
يشتغل indirect.

اذا زاد ال GABA نوم
واذا قل يدينا صرع [illegible]
[illegible] الصرع

## 2. Antagonist acting outside the binding site

- **Not structurally similar to natural agonist** → not fit the active binding site of the receptor.
- Depend mainly on **Van der Waal's interaction** in their binding.
- It may be :

Phenobarbital
خارجي الديازيبام والفينوباربيتال
ما يرتبطو على مستقبل ال GABA
وانما يرتبطو بمستقبل بجانب ال GABA
ولما ارتبطو بمستقبل بجانب ال GABA عملت تعديل لل GABA


Allosteric modulator
[illegible] الاصل
Allosteric binding site
الفرع
Binding site (open)
الأصل
Receptor
Allosteric modulation
Receptor
Binding site (shut)

[illegible] المستقبل اللي زود Allosteric

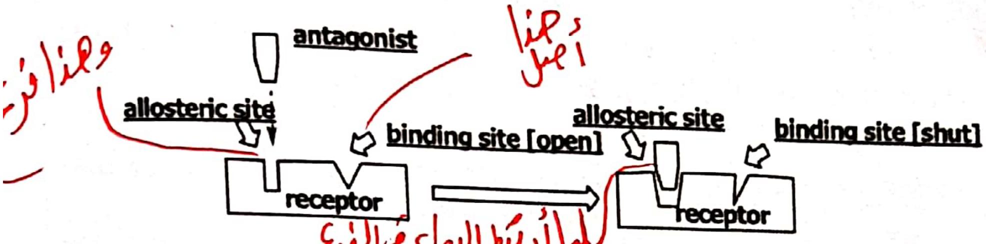
في حالة Allosteric لا يرتبط الدواء على المستقبل الأصل وانما على الفرع.
لذلك لا يمكن ان نقول The same size or The same shape
وانما نقول الى Vander Waals or hydrophobic

## a.Allosteric Antagonism:

These are **binding sites** which are located on a **different part** of the receptor surface from **the binding site,**

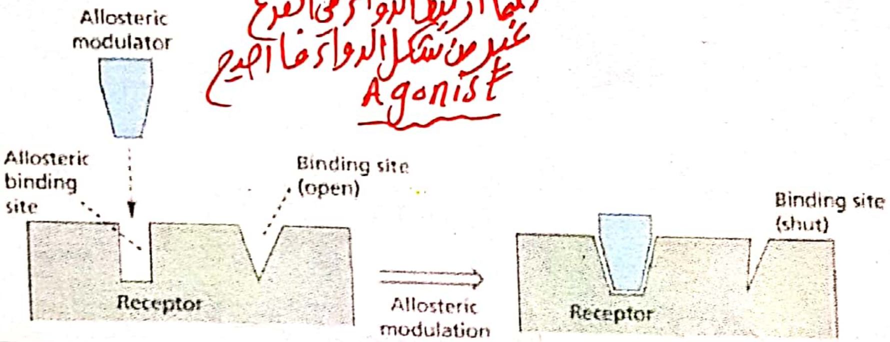
**Antagonist** bind to an **allosteric site** [a totally **different part of the receptor**] → **alter the shape** of the receptor → **distort the binding** between the **neurotransmitter** and **receptor.**

الأدوية التي تستعمل بهذا النوع أدوية CNS



antagonist
allosteric site
binding site [open]
receptor
allosteric site
binding site [shut]
receptor
وهذا فرع
هنا أصل

لما أرتبط الدواء في الفرع غير من شكل الدواء فا اصبح Agonist

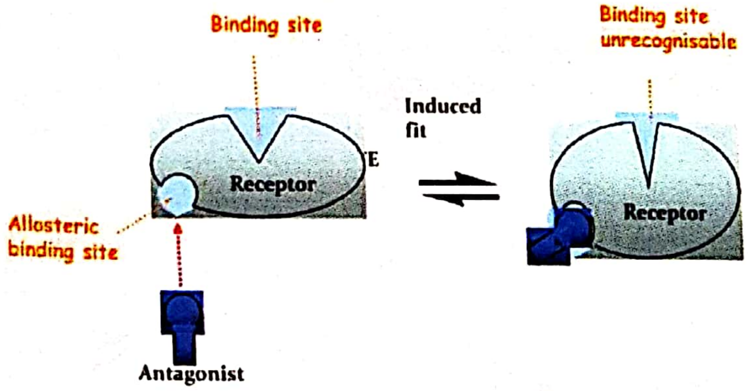


Allosteric modulator
Allosteric binding site
Binding site (open)
Receptor
Allosteric modulation
Binding site (shut)
Receptor

الدواء Allosteric أخذ high يرتبط في الفرع يا جيشي.

الـ Allosteric عكس الفكرة التي تأتي رجالين مفتاح القفل.

## a.Allosteric antagonists



Binding site
Binding site unrecognisable
Induced fit
Receptor
E
Receptor
Allosteric binding site
Antagonist

- **Antagonist binds reversibly** to an allosteric binding site
- Intermolecular bonds formed between antagonist and binding site
- Induced fit **alters the shape of the receptor**
- Binding site is distorted and is not recognised by the messenger
- **Increasing messenger concentration** does not **reverse antagonism**

مهم جدا

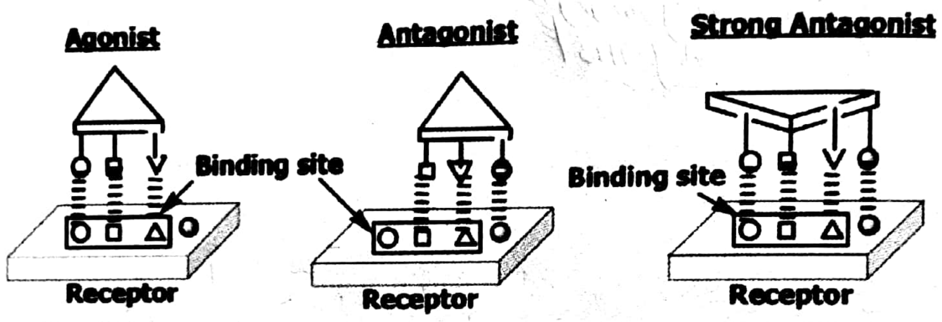
فيه أدوية تنزل زي المظله (اثار مظلة)

## b. Antagonist acting by Umbrella effect:

Rantiden

زي الفونتال د لما تنزل على المستقبل تنزل اثار مظلة.

- Some antagonists are thought to bind to regions of the receptor which are close to the normal binding site.
- Antagonists lie partially or totally over the neurotransmitter binding site forming a kind of umbrella → **prevent neurotransmitter reaching its binding site.**
- *Considered as a form of competitive antagonism,* as it affects directly the normal binding site.

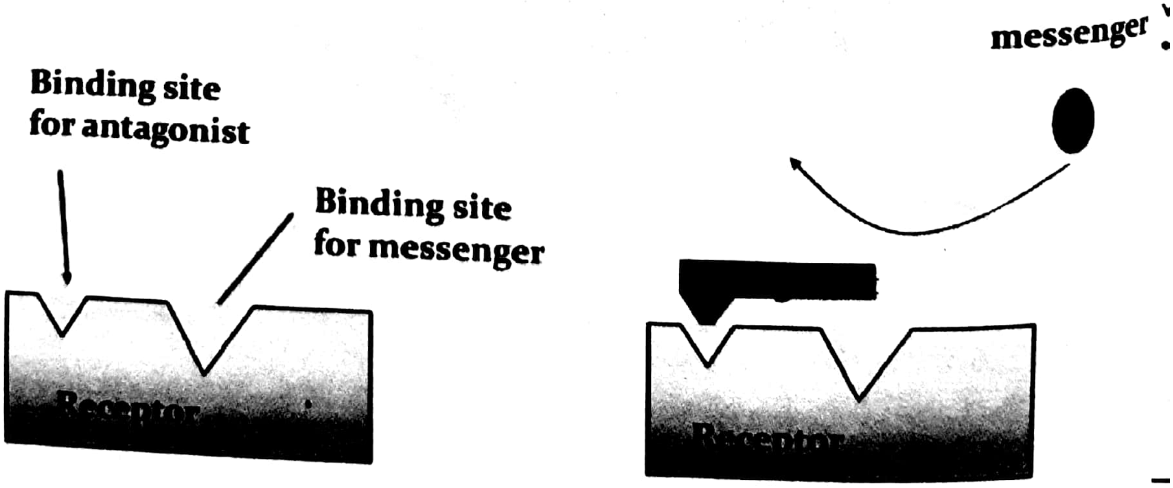

Agonist
Antagonist
Strong Antagonist
Binding site
Binding site
Receptor
Receptor
Receptor

---

مهم جدا

## Antagonists by the umbrella effect

- Antagonist overlaps the messenger binding site
- Messenger is blocked from the binding site


Binding site for antagonist
Binding site for messenger
messenger
Receptor
Receptor

Agonist يدخل يمسك في بعض المستقبلات فيعمل لبعض المستقبلات Partial ويعطي Antagonist.

# Partial Agonist (= Partial Antagonist)

لا هو ولا

**(Neither a pure agonist nor a pure antagonist)**

It's **drug which acts as an agonist** & produce **biological effect** BUT not as great as would be obtained with **a full agonist.**

قادر على الارتباط بالريسبتور بطريقتين مختلفتين من المستقبلات

The **partial agonist** may be capable of binding to a receptor **in two different** ways by using different binding regions in the binding site. **One method of binding activates** the receptor (an agonist effect), but the **other does not (an antagonist effect).**

المستقبلات كلها ترتبط بنفس ولكن ليس كلها

ولكن

**Receptors that bind the same chemical messenger** are not all the same. The **partial agonist** may be capable of distinguishing between **different receptor types** or subtypes, **acting as an agonist at one subtype,** but as an antagonist at another subtype.

قادر انه يميز بين ~~مستقبلين~~ مستقبلين واحد يشغل Agonist والثاني Antigonist

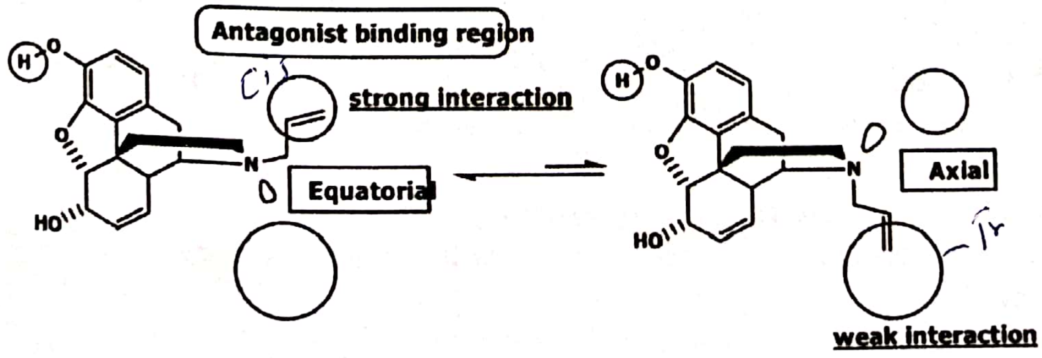
Parital activity فيه يدي لك إذا الدواء cis او Trans

Agonist ← cis

Antigonist ← Trans

**There are two models exist to explain the action of partial agonist:**

- Partial agonist may be a molecule with a perfect fit for the binding site → a very slight change in the shape of the receptor.
- Partial agonist may be capable of binding to a receptor **in two different ways**: **one type of binding activates the receptor [agonist]** while the other would **not [antagonist].**
- E.g. **Nalorphine** [partial agonist of morphine].

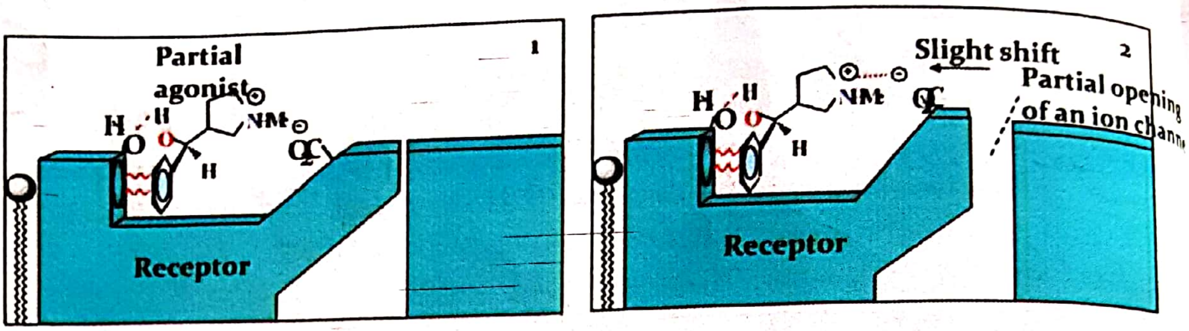


Interaction of Nalorphine with a hypothetical receptor

يخلي التشكيلات مفتوحة وأغلبها مغلقة . يسمى

## Partial agonists

Agents which act as agonists but produce a weaker effect


Partial agonist
1
H
O
H
NMe
O
O
H
Receptor
Slight shift
2
Partial opening of an ion chann
H
O
H
NMe
O
O
H
Receptor

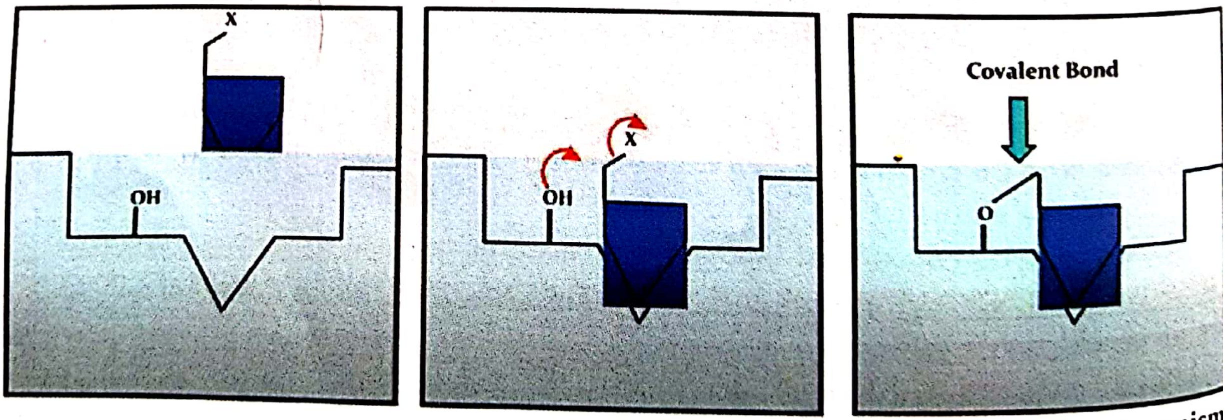
**Possible explanations**

- **Agent binds but does not produce the ideal induced fit for maximum effect**
- **Agent binds to binding site in two different modes, one where the agent acts as an agonist and one where it acts as an antagonist**
- **Agent binds as an agonist to one receptor subtype but as an antagonist to another receptor subtype**

Covalent b ← يصبح دوائك جزء من جسمك .

لكن تنزيل Receptor بـ ① acid-base
② Enzymes
③ change receptors.

## Irreversible antagonists


X
OH
OH
X
Covalent Bond
O

Irreversible antagonism

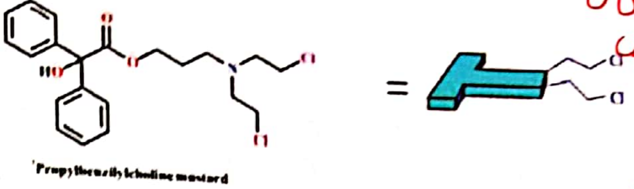
- **Antagonist binds irreversibly** to the binding site
- Different induced fit means that the receptor is not activated
- **Covalent bond** is formed between the **drug and the receptor**
- **Messenger** is blocked from **the binding site**
- **Increasing messenger concentration** does not **reverse antagonism**
- **Often used to label receptors**

الـ Agonist ← لا يمكن يعمل Covalent، مثلا لو كان ممكنا نأكل كيميائي خلقة
رب العالمين يمسك بالمستقبل بـ covalent مهاد يخرجش.
مثلا بيكون الأدرينالين لما يمسك القلب حصلك يزود يزود يزود النبض لما يتوقف.

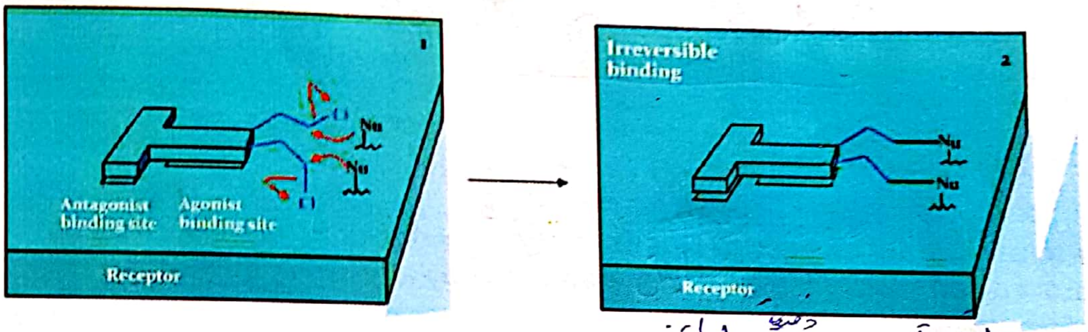
## Irreversible antagonists

covalent ≠ normal massinger

لا يوجد أي دواء ولا أي
ويكون كلما كان الـ covalent كلما كان سام
علينا ولكن احنا مضطرين
في أدوية:
→ anticancer
→ antibacterial
→ PPi , Asprine.


HO
O
N
Cl
=
Cl
Cl

Propylbenzilylcholine mustard


1
Antagonist binding site
Agonist binding site
Nu
Nu
Cl
Cl
Receptor
Irreversible binding
2
Nu
Nu
Receptor

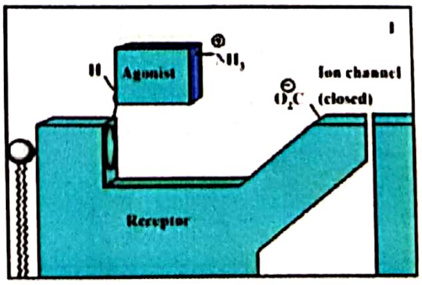
الرخيصة دقيق ١٦، ١ الساكنة

الرخصة ١,١٨ تثبيط ← تنشيط تنشيط

## (F) Desensitization (Down regulation)

Some drugs bind relatively strongly to a receptor, switch it on, but then subsequently block the receptor after a certain period of time. Thus, they are acting as agonists, then antagonists.
it is believed that prolonged binding of the agonist to the receptor results in phosphorylation of hydroxyl or phenolic groups in the receptor. This causes the receptor to alter shape to an inactive conformation, When the drug eventually leaves, the receptor is dephosphorylated and returns to its original resting shape.

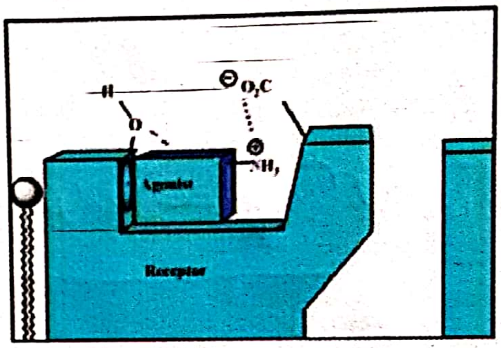
ازالة الفوسفات


1
H
Agonist
NH3
O2C
Ion channel (closed)
Receptor

- Receptors become desensititized on long term exposure to agonists
- Prolonged binding of agonist leads to phosphorylation of receptor
- Phosphorylated receptor changes shape and is inactivated
- Dephosphorylation occurs once agonist departs

## Desensitization

- Receptors become desensititized on long term exposure to agonists
- Prolonged binding of agonist leads to phosphorylation of receptor
- Phosphorylated receptor changes shape and is inactivated
- Dephosphorylation occurs once agonist departs

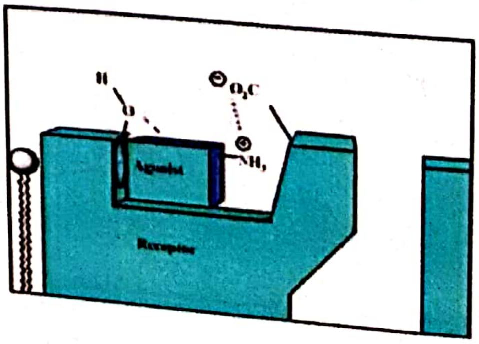


- Induced fit alters protein shape
- Opens ion channel

On **even longer exposure** to a drug, the receptor-drug complex may be removed completely from the cell membrane by a process **called endocytosis.**

## Desensitization

- Receptors become desensititized on long term exposure to agonists
- Prolonged binding of agonist leads to phosphorylation of receptor
- Phosphorylated receptor changes shape and is inactivated
- Dephosphorylation occurs once agonist departs



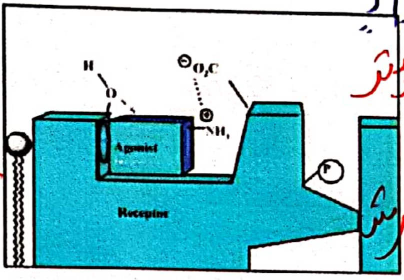
← ان الشخص يحصل عنده زيادة في عدد المستقبلات وبالتالي يحتاج الى جرع عالية
من المادة المدمن عليها.
أعطا الشخص تدريجيا من المادة التي أدمن عليها حتى تبدأ الخلية تسحب أو تلغي المستقبلات
زيادة شوية شوية وترجع الخلية لحالتها الطبيعية.

# Desensitization

- Receptors become desensititized on long term exposure to agonists
- Prolonged binding of agonist leads to phosphorylation of receptor
- Phosphorylated receptor changes shape and is inactivated
- Dephosphorylation occurs once agonist departs

تعود الادمان نوعين
inhibition عادة زي القات السو
الشاي - الحلويات =
الادمان ← الاحساس بأشياء كثير
طبيعية.

ادمان أصله Tolarance
كل Tolarance أصله ادمان لا
الادمان يحصل في الاماكن التي تؤثر
الجسم بشكل كامل زي CNS
per ما يسكة عضو معين ما تؤثر
الجسم بالكامل.



- Phosphorylation alters shape
- Ion channel closes
- Desensitization

الخلية وزودتها كلما زودت مستقبلات زيادة (Tolarnce)

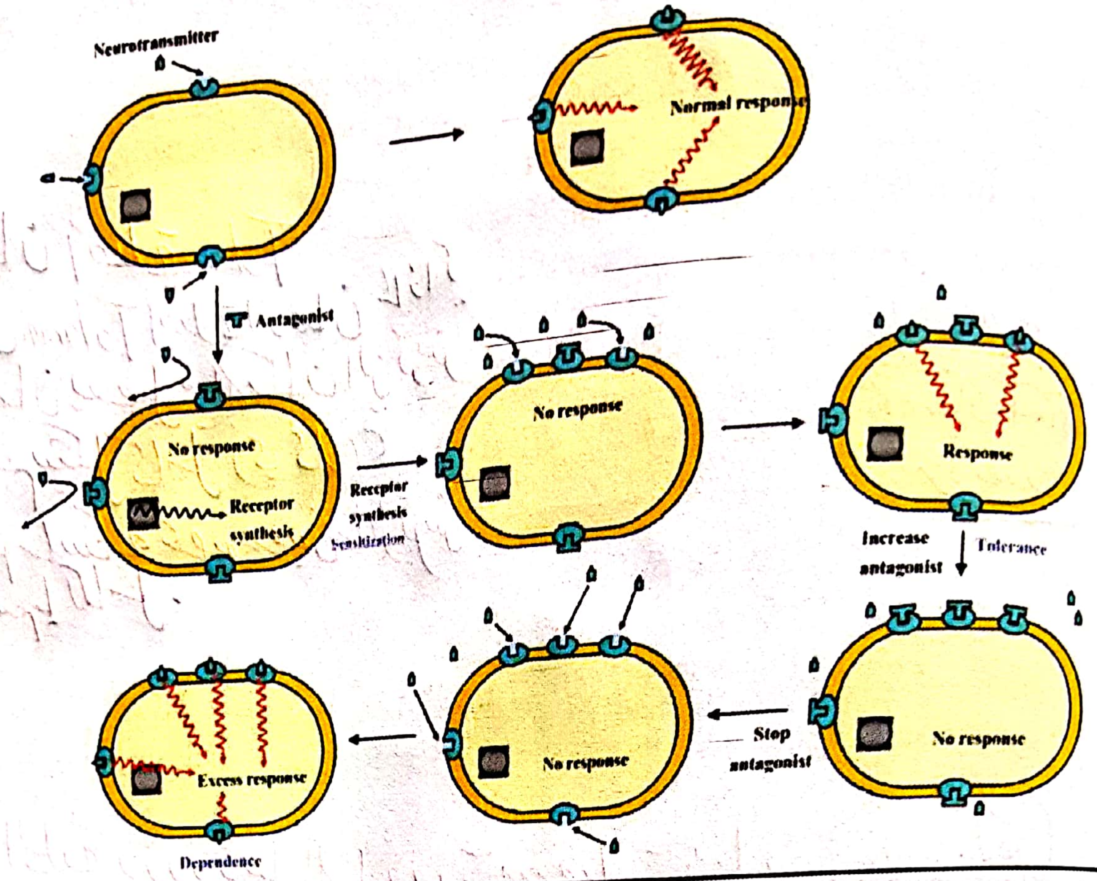
heroin
تثبيط مثل ← morphin morphin
النهاية 1,22
تثبيط تثبيط ← تنشيط

## ② Sensitization (Up regulation)

- Receptors become **sensititized** on long term exposure to **antagonists**
- Cell synthesises more **receptors to compensate for blocked receptors**
- Cells become more sensitive **to natural messenger**
- Can result **in tolerance and dependence**
- Increased doses of antagonist are required to achieve same effect **(tolerance)**
- **Cells are supersensitive to normal neurotransmitter**
- Causes withdrawal symptoms **when antagonist withdrawn**
- Leads to dependence

**Tolerance is** a situation where **increased doses** of a drug are required over time to achieve the same effect.
D**ependence is related to the body's ability to adapt to the presence of a d**rug.
On stopping the drug, withdrawal symptoms occur as a result of abnormal levels of target receptor.

## Sensitization


Neurotransmitter
Normal response
Antagonist
No response
Receptor synthesis
Receptor synthesis
Sensitization
No response
Response
Increase antagonist
Tolerance
No response
Stop antagonist
No response
Excess response
Dependence

## Drug dependence

- It usually occurs after administration of CNS acting drugs.
- Is a phenomena related to tolerance.
- It involves a certain degree of tissue adaptation.
- Withdrawal ofthe drug could produce certain unpleasant symptoms.
- **Types of dependence:-**

| Habituation | Addiction |
|---|---|
| - Mild degree of drug dependence.<br>- ***Psychic*** dependence.<br>- When drug stopped → develop some emotional distress for a relative short period.<br>- E.g. Smoking and Coffee. | - More serious form of drug dependence.<br>- ***Psychic*** and ***physical*** dependence.<br>- When drug stopped → Withdrawal symptoms → reverse the normal pharmacological action<br>- E.g. Morphine and Heroin |

Which of the following would up-regulate postsynaptic $\beta_1$ adrenergic receptors?

A. Daily use of amphetamine that causes norepinephrine to be released.

B. A disease that causes an increase in the activity of norepinephrine neurons.

C. Daily use of isoproterenol, a $\beta_1$ receptor agonist.

D. Daily use of formoterol, a $\beta_2$ receptor agonist.

E. Daily use of propranolol, a $\beta_1$ receptor antagonist.

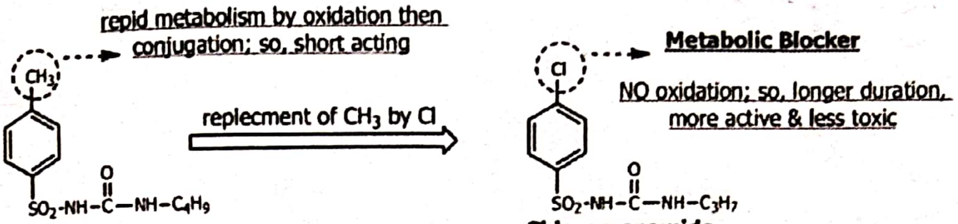
**BIOISOSTERES**

**[i] Classical Bioisosteres** **[ii] Non-Classical Bioisosteres**

# [i] Classical Bioisosteres

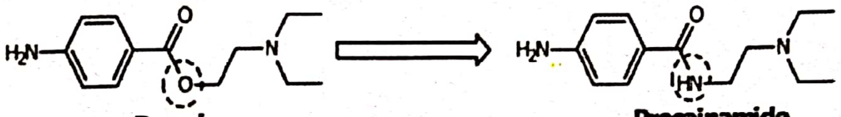
***Must have the same shape, size & outer electronic configuration.*** **It's subdivided into:**

## 1. Monovalent atoms or groups ( $-CH_3$ , $-NH_2$ , -OH , -Cl , -F ):


repid metabolism by oxidation then conjugation; so, short acting
$CH_3$
replecment of $CH_3$ by Cl
$SO_2-NH-\overset{O}{\overset{\|}{C}}-NH-C_4H_9$
Metabolic Blocker
NO oxidation; so, longer duration, more active & less toxic
Cl
$SO_2-NH-\overset{O}{\overset{\|}{C}}-NH-C_3H_7$

**Tolbutamide** [ oral hypoglycemic ] **Chloropropamide**

## 2. Divalent atoms or groups ( $-CH_2$, -NH , -O- , -


$H_2N$
O
O
N
$H_2N$
O
HN
N

**Procaine**

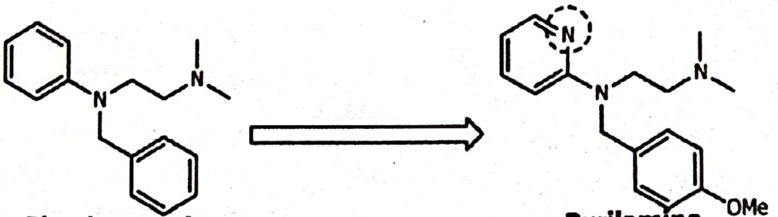
[ local anesthetic with membrane stabilizing properties ]

hydrolyzed rapidly by esterase

**Procainamide**

less hydrolyzed

## 3. Trivalent atoms or groups ( -CH= , -N= , -P= ):



**Phenbenzamine**

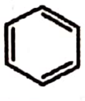
[ anti-histaminic ]

**Pyrilamine**

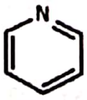
( more potent anti-histaminic )

## 4. Ring equivalents:

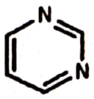
Rings with the ***same B.P(boiling point)*** are used as isosteres; ***they have nearly the same dipole moment*** & nearly the same chemical & physical properties.



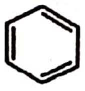
**Benzene**



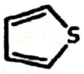
**Pyridine**



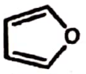
**Pyrimidine**



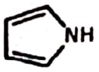
**Benzene**



**Thiophene**



**Furan**



**Pyrrole**

# Steric features of drugs

**Efficiency of drug receptor interaction is influenced by stereochemistry of drug & receptor.**

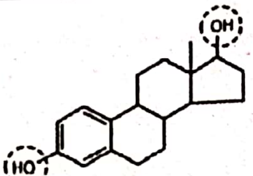
**Steric features may be:**

**1.Geometrical isomerism.**
**2.Conformational isomerism.**
**3.Optical isomerism.**

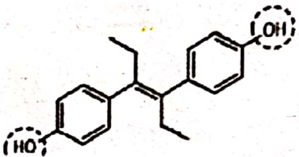
## 1. Geometrical Isomerism

**Geometric isomers are either Cis or Trans**

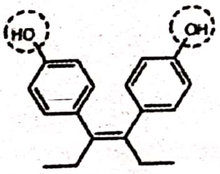
E.g.
***Trans- Diethyl stilbsterol*** **(non-steriodal estrogene)**[DES] is ***14 times more active than Cis isomer***, as the distance between the two OH groups in trans-DES is ***approximately equal that in Estradiol*** while in cis isomer is totally different.



**Estradiol**



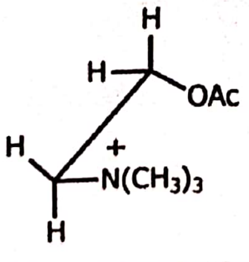
**Trans-DES**



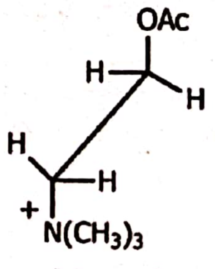
**Cis-DES**

## 2. Conformational isomerism

**E.g.2:**
**Acetyl choline acts at two receptors; muscarinic & nicotinic**
**•Cisoid conformer: interact with nicotinic receptors.**
**•Transoid conformer: the best for muscarinic receptors.**



**Cisoid conformation**

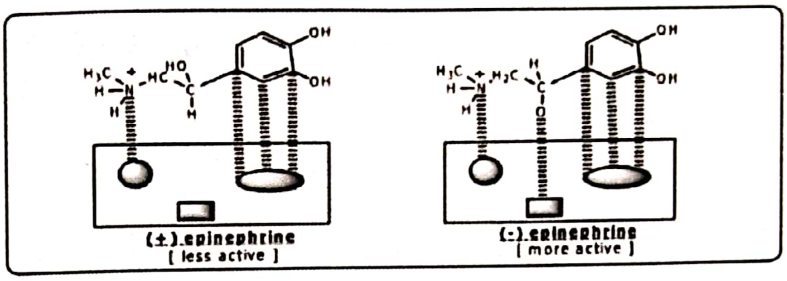


**Transoid conformation**

# 3. Optical isomerism

**Optical isomers:**
**Molecules capable of *rotating plane polarized light* in opposite direction.**

**Enantiomers:**
**Non super-imposable mirror images with the same physical & chemical properties but not the same spatial shape → NO similar interaction with the receptor.**



(±) epinephrine
[ less active ]

(-) epinephrine
[ more active ]

**N.B:**
**Most chiral drugs are synthesized as a mixture of *both mirror images [racemate]*; *usually only one enantiomer interacts with the receptor*, the *other may interact with a totally different receptor causing side effects.***

**E.g.**
**Racemic Thalidomide [sedative] → reacted elsewhere in the body as a poison [teratogenic**

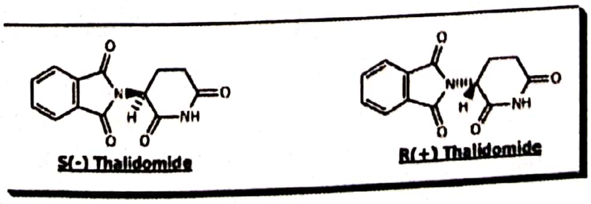
---

# Thalidomide

**•This drug was appeared in Germany [1957] as sedative & said to be safe for pregnant women to be used for morning sickness.**

**•But after its use ; it was found that it's TERATOGENIC [especially for limbs→ inhibition of growth → phocomelia ] ; this is because morning sickness appear around the time of foetal limb growth.**

**•It was found that S(-) isomer of Thalidomide was responsible for Teratogenic effect , DNA intercalation [while R(+) isomer devoid of this side effect]**



S(-) Thalidomide

R(+) Thalidomide

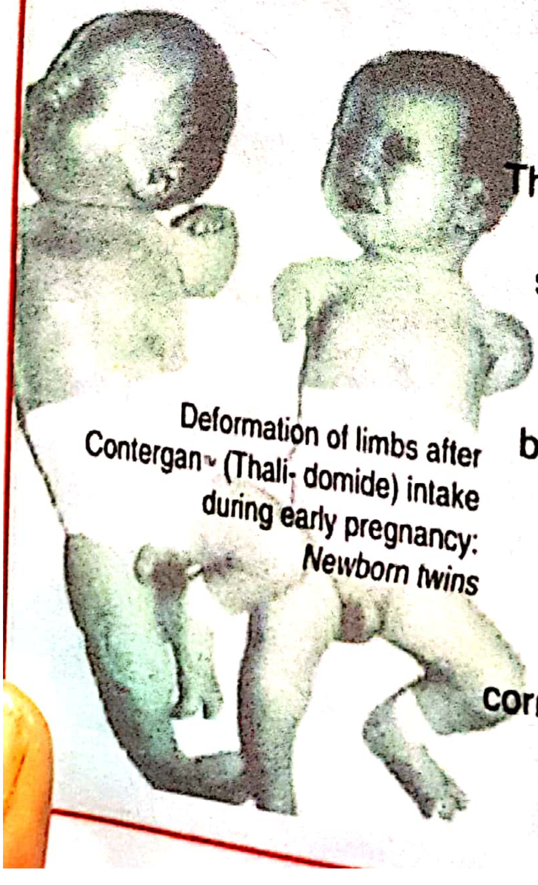
**In 1965** , by using thalidomide for a leprotic patient as sedative, it was found that it has **anti-inflammatory** effect by stoping body over-reacting & suppressing the body defences

- **In 1998** , FDA approved Thalidomide for treating **ENL [Erythema Nodosum Leprosum]** in leprotic patients → loss of feeling which can lead to paralysis.

- They now discover structurally related compounds show about 4000 times its potency & with much lower side effects.

---

## The Thalidomide Story



Deformation of limbs after Contergan® (Thali- domide) intake during early pregnancy: *Newborn twins*

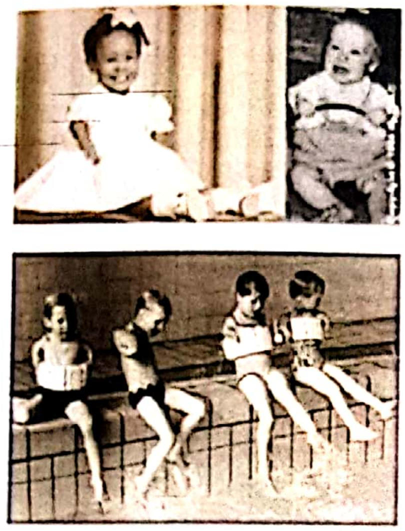
Thalidomide first appeared in Germany on 1st October 1957. It was marketed as a sedative with apparently remarkably few side effects.

The Drug Company who developed it believed it was so safe it was suitable for prescribing to pregnant women to help combat morning sickness.

It was quickly being prescribed to thousands of women and spread to most corners of the globe. Nobody had any idea of what was to follow.

Drug testing proc

## The Thalidomide Story

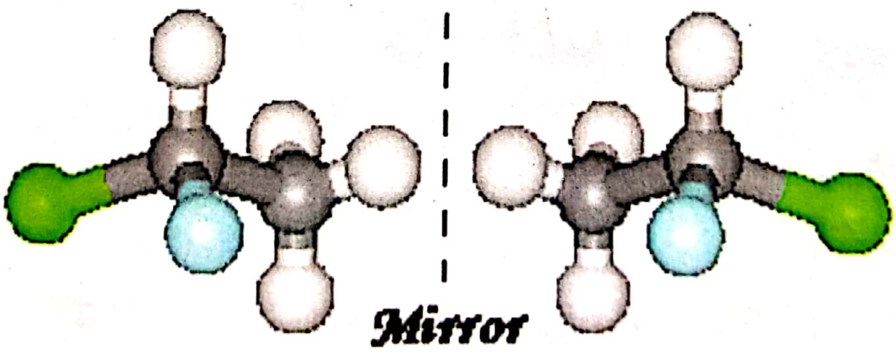


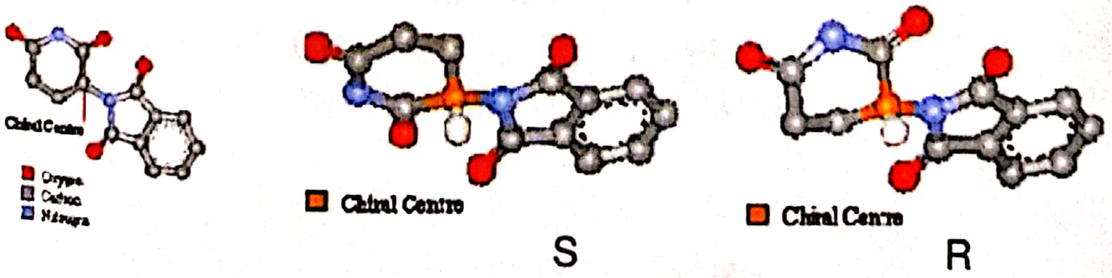
*'Thalidomide Babies'*
Pictured left are some of babies born with the flipper-like limbs. Remarkably, many of the children involved have gone on to lead successful and fulfilling lives.

Around 12,000 children were born with some kind of disability due to damage caused by thalidomide. Countless more miscarriages, which weren't recorded as caused by thalidomide, mean we can't assess correctly the true scale of the disaster. Estimates put the number of children affected at around 20,000. Even this doesn't take account of the families of the children affected.

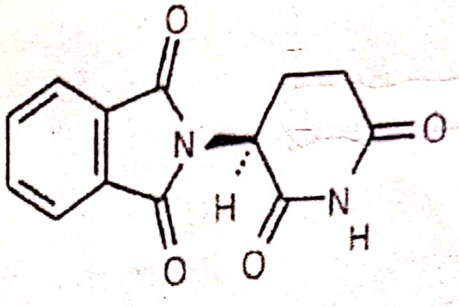
---

## Thalidomide: Racemate vs. isomer ?

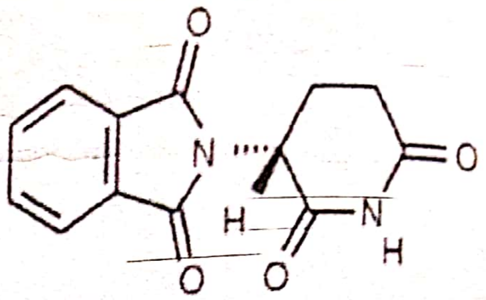



Chiral Centre
🟥 Oxygen
▨ Carbon
🟦 Nitrogen
🟧 Chiral Centre
S
🟧 Chiral Centre
R

# Thalidomide: Racemate vs. isomer ?



*S*-(-)-thalidomide

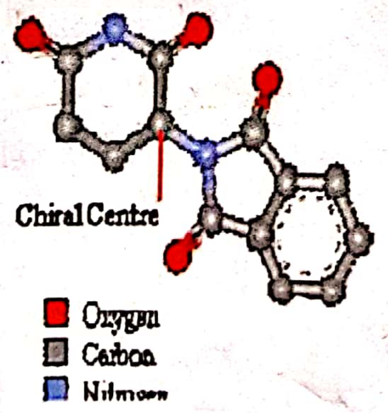


*R*-(+)-thalidomide

| | | |
|---|---|---|
| *yes* | Teratogenic | *no* |
| *yes* | DNA intercalation | *no* |
| *yes* | Binding to dG | *no* |

---

## The Thalidomide Story



Laboratory tests after the thalidomide disaster showed that in some animals the 'S' enantiomer was teratogenic, but the 'R' isomer was an effective sedative.

It is now known that even when a stereo-selective sample of thalidomide (only one of the optical isomers) is created, if

## The Thalidomide Story

### Thalidomide Today

In 1998 the FDA gave approval for thalidomide to be marketed for the treatment of erythema nodosum leprosum (ENL), a complication of leprosy, a disfiguring skin disorder involving loss of feeling that can lead to paralysis. This type of leprosy affects only a few thousand people in the U.S. (although more in the rest of the world), but now that the drug is approved, physicians can prescribe it for many more people with other conditions.

According to a recent survey, two-thirds of people of childbearing age are not familiar with thalidomide. **Because thalidomide may become more available to women capable of having children, they need to be warned about the serious risks of birth defects.**

# Drug Metabolism

# 1

## Medicinal Organic Chemistry
## and
## Drug Design

By
Ass Prof .Mokhtar Al-Ghorafi

27 الدفعة
(العاصفة الحاسمة)

# Drug Metabolism

## Metabolism [Biotransformation]:

أي حاجة غريبة
سواء دواء
او سم فالكبد
يتعامل معاها

•Xenobiotics are excreted either unchanged or after biotransformation. [Xenobiotics: drug & foreign compounds to body]

•**Drug metabolism**: A process, by which drugs are rendered more water soluble, less reabsorbed → more excreted → **Detoxification**.

## But metabolism may cause other effects:

أكثر شيوعاً الدواء ان يتحول من active الى inactive

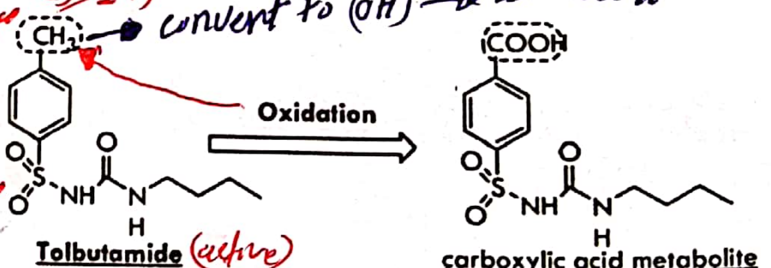
**1.Formation of inactive or less active metabolite from active drug: [M COMMON]**

### Example 1:

ميثيل نشيل الاكسيد (أليفاتي)

convert to (OH) → to COOH

اليفاتي.
→ method → oxidation
→ enzymes → cyto P 450
→ results → acid

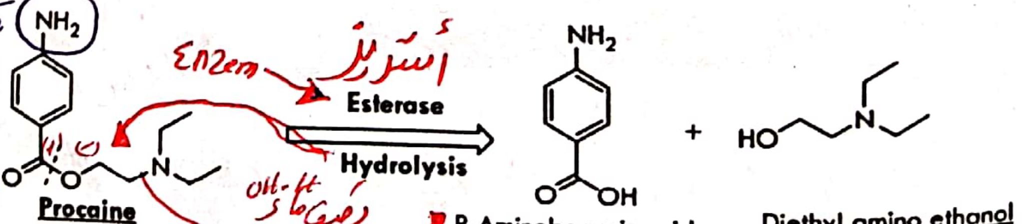


**Tolbutamide** (active)
[oral hypoglycemic]

**carboxylic acid metabolite**
[inactive metabolite]

### Example 2:

Polar قوية
عاليها عندنا فوائد
ال و ميثيل N



**Procaine**
[Local anesthetic]

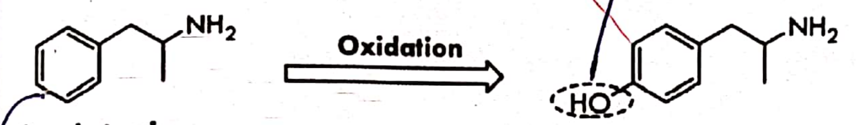
الطريقة → Hydrolysis

**P-Aminobenzoic acid** + **Diethyl amino ethanol**
[inactive metabolites]

اذا كان معانا حلقة benzen يعطي Epoxid بعد ذلك الى فينول ع

هنا كان في طريقة واحدة OH
اذا اكتب في الامتحان 2-OH
صح

### Example 3:


NH2
Oxidation
NH2
HO

**Amphetamine**
[CNS stimulant]

**P-Hydroxy amphetamine**
[less active metabolite]

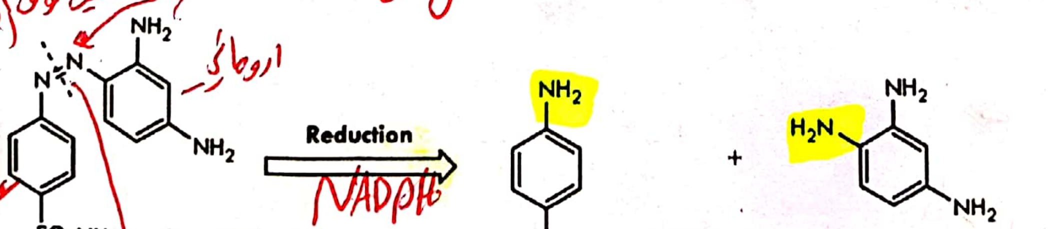
بنزين —انزيم→ epoxid → phenol

2 ← تحويل الدواء من inactive الى active مثلا الدواء يكون (Prodrug)

## 2. Formation of active metabolite from initially inactive drug [Prodrugs]:

### Example 1:

غير مهمة اكتب فوق الـ → method → Reduction
Enzyme → NADPH


NH2
N
N
NH2
SO2NH2
Reduction
NADPH
NH2
SO2NH2
+
NH2
H2N
NH2
اروماتك

**Prontosil red**
[inactive]

**Sulphanilamide**
[anti-microbial]

high polar

**Triamino benzene**

اي رابطة [illegible] N تفكها وتضيف معاها ع الروابط [illegible] H2 تصير NH2

تحويل الدواء من active ال Co-active

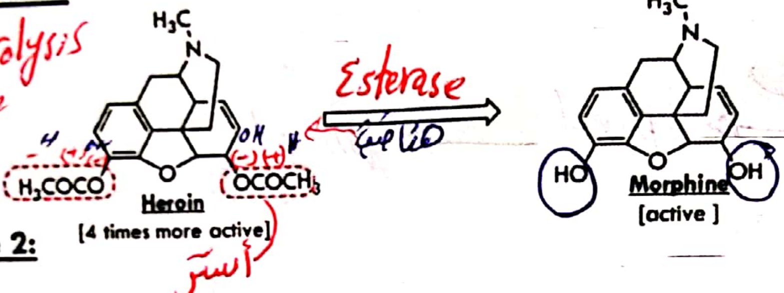
## 3. Formation of active metabolite from initially active drug [Co-activation]:

ع الامتحان

Enzymatic biotransformation doesn't always terminate its action.

**Example 1:**

method → hydrolysis
enzyme → Estrase
result → OH



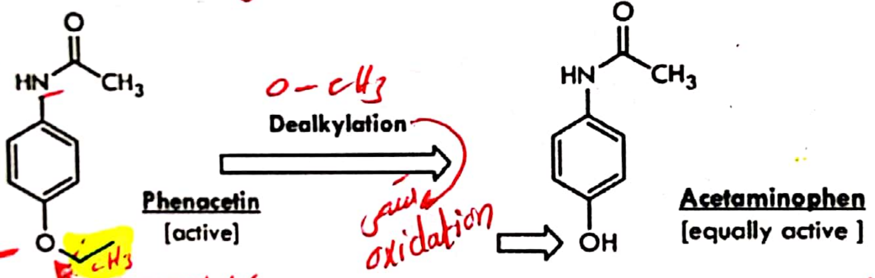
H₃C
N
OH
H
H₃COCO
OCOCH₃
Esterase
تحلل مائي
HO
OH

**Heroin**
[4 times more active]
أستر

**Morphine**
[active ]

**Example 2:**

أو ما شي على O و N



O
HN
CH₃
O
CH₃
O-CH₃
Dealkylation
يسمى oxidation
HN
CH₃
OH

**Phenacetin**
[active]

**Acetaminophen**
[equally active ]

إذا O-CH₃ حاجة بجانبها اريد تشيلها

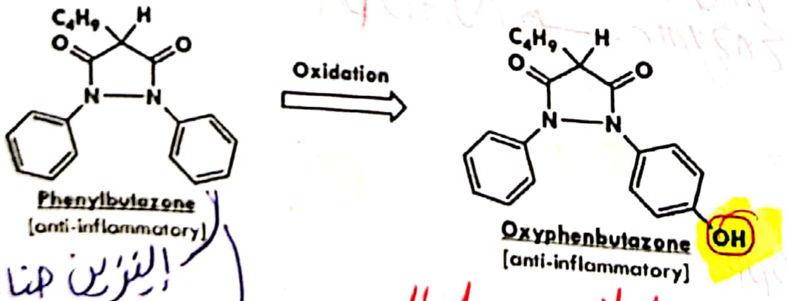
شيلها وحطينا مكانها (H)

oxidation = dealkylation
نفس

---

## 3. Formation of active metabolite from initially active drug [Co-activation]:

**Example 3:**



C₄H₉
H
O
O
N
N
Oxidation
C₄H₉
H
O
O
N
N
OH

**Phenylbutazone**
[anti-inflammatory]

**Oxyphenbutazone**
[anti-inflammatory]

إذا لها para هنا البنزين
اسهل منطقة فاعلية
الكبد لا يستطيع يعمل للحلقتين
مع بعض يبدأ بالحلقة الأولى
اذا متغمس يطلع للثانية

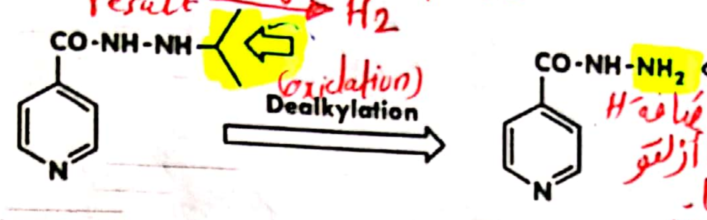
method → oxidation
Enzy → Cyto P-450

① تحويل الدواء من active إلى another active.
قاعدة ← أي حاجة بجانب ال N شيلها وضيف H

## 4. Formation of active metabolite having a pharmacological action different from parent drug:

طريقة ← 1 method → Dealkylation
Enzym → cytochrom P-450
result → $H_2$

**Example 1:**


CO-NH-NH
N
(oxidation)
Dealkylation
CO-NH-NH₂
N

**Ipronioazide**
[anti-depressant]

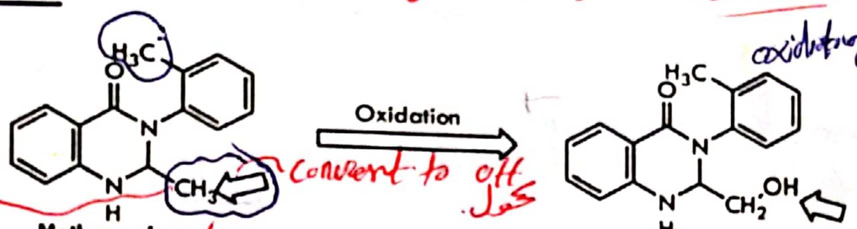
**Isoniazide**
[anti-T.B.]

لماذا أدا المعروف أن في هذه الحالة أضافة H لماذا أعملنا oxidation؟

في هذه الحالة شلتو كربونات وليس إضافة H الذي قام بهذه العملية cyto عندما أزلتو الكربونات حل بدلها H عوضًا عنها.
عندما أزلت الكربونات جاء NADPH عوض كانت عملية oxidation-reduction reaction والتي تسمى Dealkylation

لأنه لا يمكن أن تحصل oxidation إلا وحدث معها reduction

**Example 2:**


H₃C
O
N
N
H
CH₃
convert to OH
تحول
Oxidation
H₃C
O
N
N
H
CH₂OH

الفارق

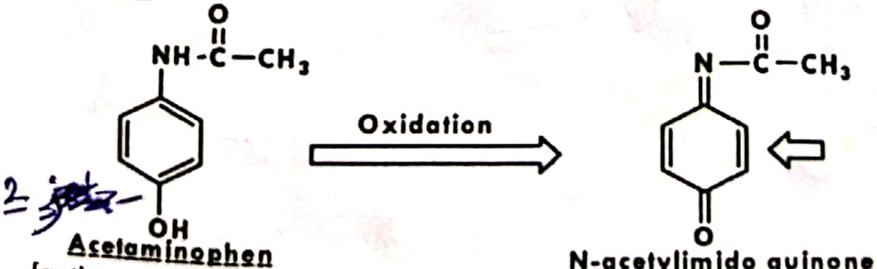
**Methaqualone**
[sedative-hypnotic]

**2-hydroxy methyl metabol**
[hypolipidemic]

method → oxidation
Enzym → cyto P-450

## 5. Formation of toxic metabolite from initially less toxic drug

**Example 1:**

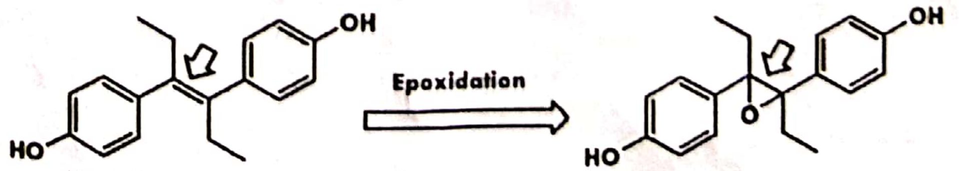

O
NH-C-CH₃
OH
Oxidation
O
N-C-CH₃
O

phase 2 ~~[illegible]~~

**Acetaminophen**
[antipyretic-analgesic]

**N-acetylimide quinone**
[toxic metabolite]

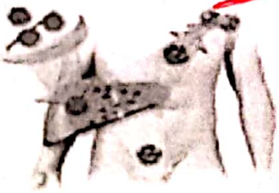
**Example 2:**


OH
HO
Epoxidation
OH
O
HO

**Diethyl stilbsterol [DES]**
[anti-cancer]

[carcinogenic epoxide metabolite]

## Sites of drug metabolism:

| ① In liver [ Hepatic ] | ② Extra-Hepatic |
|---|---|
| - **The main site of metabolism** as it's full of **metabolizing enzymes.**<br>- **1st Pass Effect:**<br>Orally administered drugs [most of drugs] → pass through the liver before being absorbed & reaching the systemic circulation.<br> | - As intestinal mucosa, kidney, lung.<br>- **Intestinal bacterial flora** in the intestine play role in drug metabolism :<br>1. **Catalyze hydrolysis of conjugated compounds eliminated in bile.** E.g. bacterial sulfatases hydrolyzed sulfate conjugation of **Premarin** [oral estrogen] giving free estrogen which reabsorbed from intestine into portal circulation.<br>2. **Reduction of nitro group in nitroimidazole & azo group of azides.** E.g. **Sulfasalazine** [anti-infective & anti-inflammatory used in ulcerative colitis] → reduced by bacteria in colon → 5-amino salicylic acid + sulphapyridine. |

Frome less polar to high polar

**Metabolism**

**Phase I**
**[Functionalization Reactions]**

**Phase II**
**[Conjugation Reactions]**

**•The purpose of Phase I is to make drug more polar → readily excreted**

➢ **It's performed to:**

1. **Introduce new functional gp** [e.g. aromatic &aliphatic hydrolxylation].
2. **Modify existing functional gp** [e.g. rduction of ketones & aldehydes to alcohols / oxidation of alcohols to acids / hydrolysis of esters to acids]
3. **Expose a functional gp [Acceptor site] for phase II**

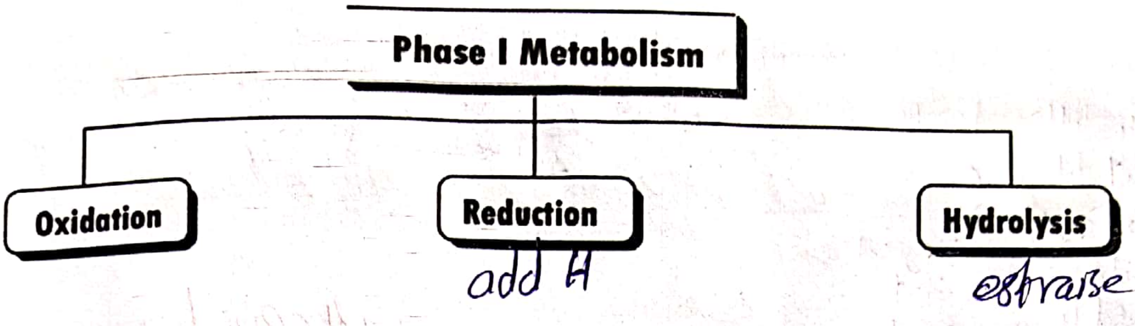
They are enzymatic reactions where **functional groups as OH, $NH_2$ groups are masked by addition of new polar endogenous group** → ↑ **solubility & excretion.**

**Most of drug undergo both phase1 and 2**

**N.B:**

**•Xenobiotics that are resistant to metabolizing enzymes are already hydrophilic → excreted unchanged.**

**•Some drugs may pass directly into phase II.**



## Phase I Metabolism

- **Oxidation**
- **Reduction**
  - add H
- **Hydrolysis**
  - estrase

B6 — NADPH

## [I] OXIDATION REACTIONS

- The **most common** reaction for drug metabolism.
- Catalyzed by group of **membrane-bound mono-oxygenase enzymes** found in cytoplasmic reticulum of **liver** & **other extra-hepatic tissues.** كثير
  - These mono-oxygenases are called: **Cytochrome P-450 mono-oxygenase enzyme system [CYP-450]** or **Mixed Function Oxidases [MFO] are able to add polar groups to a wide varity of drugs** قطبية
    cyto مسئول عن نقل الاكسجين الى الدواء
    - **They are made of several components:**
    - **Cytochrome P-450:** heme protein responsible for transferring an oxygen atom to the substrate RH. [This reaction needs NADPH as reducing agent].
      دواء cyto كوانزيم الذي يساعد V-B6

$$RH + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P-450}} R\text{-}OH + H_2O + NADP^+$$

oxidation - Reduction → Reaction

اول ما يقوم cyto يضيف O
يقوم NADPH يضيف H

⑨ **1.NADPH-dependent cytochrome P-450 reductase.**
**2.NADH-linked cytochrome $b_5$.**

With cofactors NADPH & NADH → **supply electrons** "reducing equivalents" needed in overall oxidation reactions.

## ① Oxidation of Aromatic rings [Arenes ] [Aromatic Hydroxylation

- **The major route of drugs having Benzene rings [aromatic compounds = arenes].**

- **Phenolic metabolites [Arenols] are produced.**

يتحول ال epoxid الى الفينول

- **It's done through formation of epoxide intermediate [Arene oxide] → rearrange spontaneously to phenolic product.**

- The **arene oxide** is **highly toxic** due to its **electrophilic** characters → **bind to any nucleophile** in the body [DNA, RNA or Protein] → **cellular damage.**

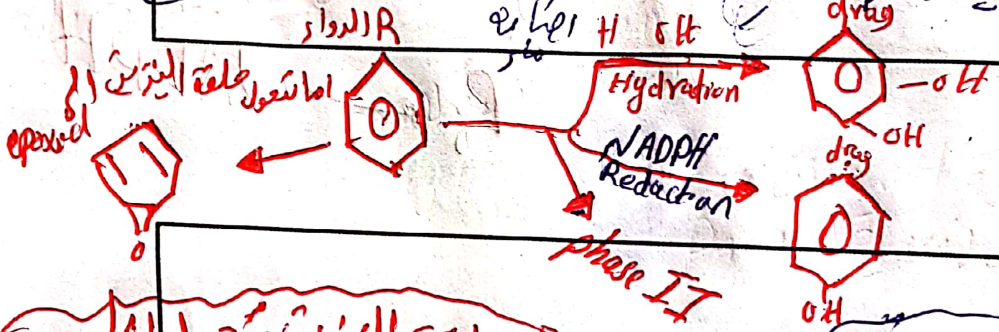
ازالة السمية او حلقة البنزين تتحول الى

- **Detoxification is done through:**

**[i] Spontaneous rearrangement to phenols [major]**

② **[ii] Enzymatic hydration to trans-dihydrodiols.**

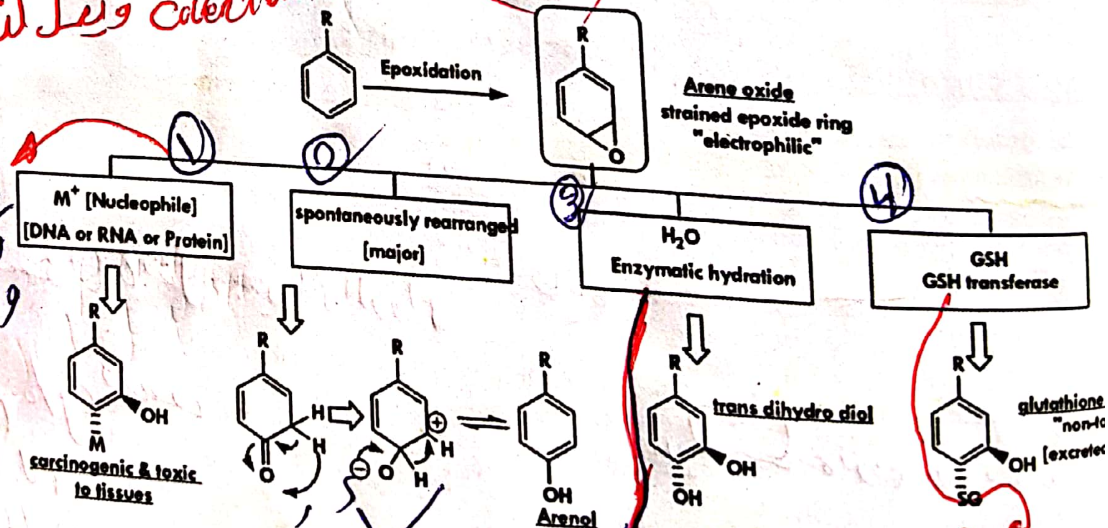
③ **[iii] Enzymatic conjugation with GSH.** – phase 2



R الدواء
H OH
drug
اما تتحول حلقة البنزين الى epoxid
Hydration
NADPH
Reduction
-OH
OH
drug
OH
phase II

حلقة البنزين بتتحول الى epoxid
ويروح epoxid يتفاعل مع covalent bond ويعمل لنا مشاكل

دواء



R
Epoxidation
R
O
Arene oxide
strained epoxide ring
"electrophilic"
①
M⁺ [Nucleophile]
[DNA or RNA or Protein]
R
OH
M
carcinogenic & toxic to tissues
②
spontaneously rearranged
[major]
R
O
H
H
R
O
H
H
R
OH
Arenol
③
H₂O
Enzymatic hydration
R
OH
OH
trans dihydro diol
④
GSH
GSH transferase
R
OH
SG
glutathione
"non-to
[excreted

ويعمل لنا مشاكل

أو تتحول الى الفينول

NADPH عن طريق

Cyto-P-450 Hydration

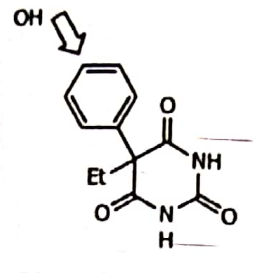
phase II عن طريق glucuronic acid

① ← اذا معاك حلقة البنزين يحدث الاسئوال في para

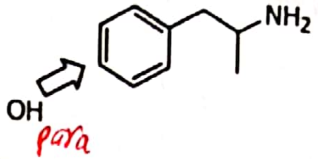
اذا فيه زحمة في para يرجع ortho

## Rules of Aromatic Hydroxlyation:

1.If mono-substituted aromatic ring → Para-Hydroxylation usually predominate > ortho.



Phenobarbital



para

Amphetamine

ملاحظة

اذا الدواء معندوش S, O, N جاهزة لا يمكن يدخل phase II

لازم مثلا يكون عندك NH او OH جاهزة

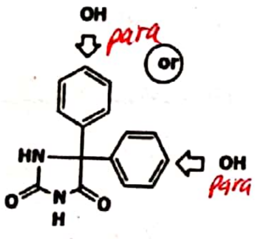
جاهزة

وتذكر عندما كنت اقول لك ضيف O ~~[illegible]~~ او زيل H على شان أجهز الدواء لـ phase 2

2 ← اذا معاك حلقتين ابدأ بالحلقة الاولى اذا متفعش أعمل للحلقة الثانية

لو اذا متفعش يروح phase II

2.If the compound with two identical aromatic rings → oxidation of one ring only.

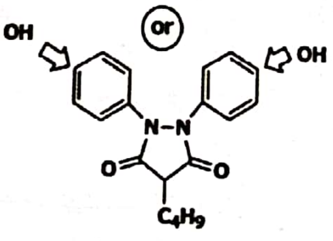


para

or

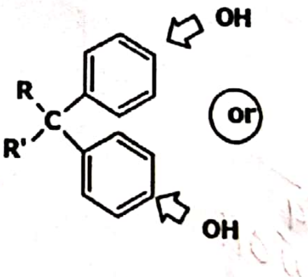
para

Phenytoin



or

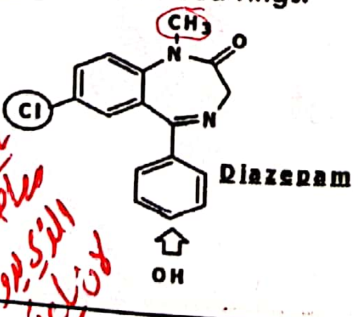
Phenyl butazone



or

③.Hydroxylation is more rapidly in electron-rich rings [with electron-donating group] → activated rings.

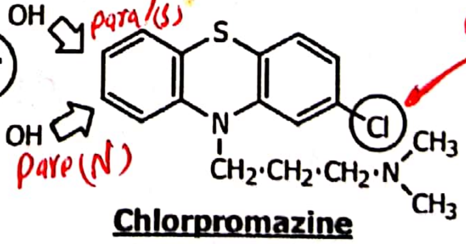
حلقة بدون افضل حط لها OH



Diazepam

اذا معاك حلقتين وحلقة فيها Cl ساحب اعمل على الحلقة الي بدون ساحب لان Cl ساحب

or



para (S)

pare (N)

Chlorpromazine

ساحب

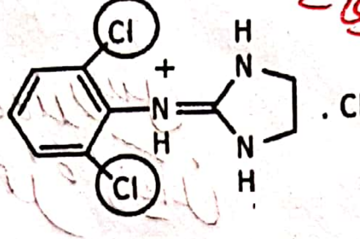
Cl

اذا معاك حلقة فوقها S, N وحلقة فيها Cl الي فيها S, N افضل واسهل

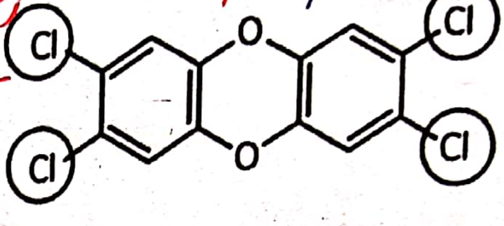
**4.Deactivated aromatic rings** [with **electron-withdrawing group** as Cl, NO2, COOH…] → **no**
**hydroxylated or slowly hydroxylated**.

صعب الأيض. زي هذا المركب يدفع انتباهات الكل لأنه فيه مجموعات ساحبة

high toxic

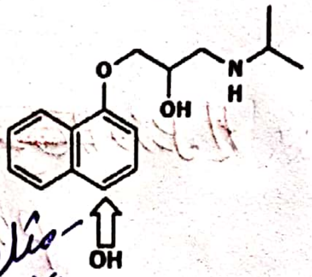


**Clonidine HCl**



5.If the drug with **two aromatic rings** → hydroxylation **occurs in the more electron-rich ring & usually one ring is attacked.**

الهما أسهل حلقة من
دون او حلقة معاها
O ع حلقة معاها O
لأنها مجموعة دافعة

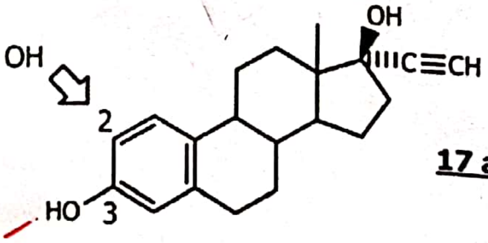


**Propranolol**

مثلا اذا كان para محجوز ترجح ortho نسبة للpara

اذا كان ال para فيه OH وانت تشتغل Hydroxylation زيادة OH اخرى تكون ortho بنسبة للpara

6.Hydroxylation occurs at **ortho position** if para position is **occupied**.



**17 alpha-ethinyl estradiol**

para محجوز تدخل OH على ال ortho

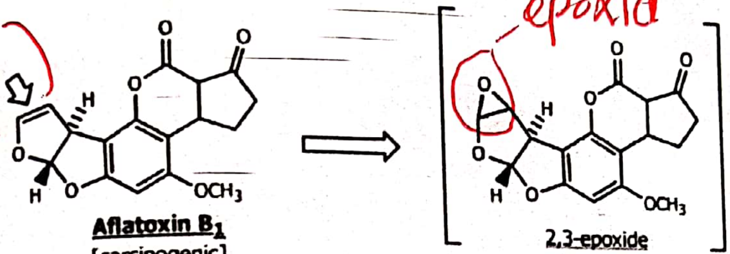
بعض الفطريات تطلع مواد aflatoxin

## ② Oxidation of Olefins

- Some epoxides are **toxic** → extremely **reactive** & bind easily to proteins, DNA & RNA. For E.g. **Aflatoxin $B_1$** [carcinogenic agent formed by *Asperigillus flavus* growing on pea nut] & **Stilbene, Diethyl stilbsterol**.

معظم أشكال

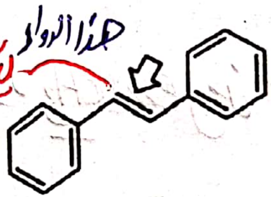
// لما يكون معاك دبل يطلع epoxid


H
O
O
O
O
H
O
$OCH_3$
O
O
O
H
O
H
O
$OCH_3$
O
epoxid

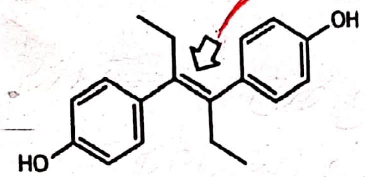
**Aflatoxin $B_1$**
[carcinogenic]

**2,3-epoxide**

هذا الدواء يتحول الى epoxid



**Stilbene**



**Diethyl Stilbsterol [DES]**

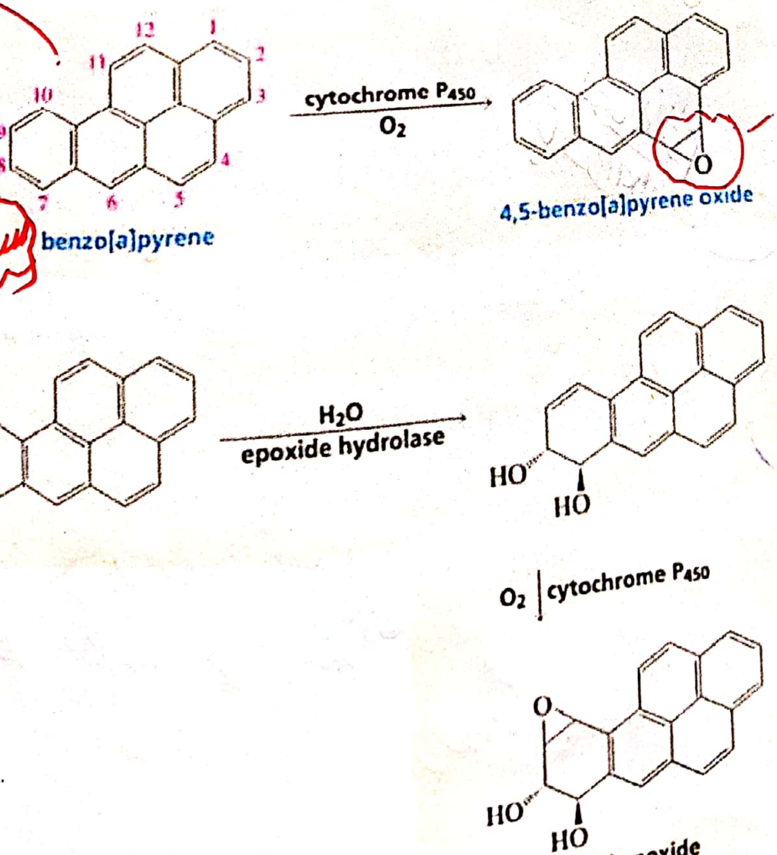
يتحول الى epoxid
= لأنه فيه دبل

Trat Brest cancer

معظم الأدوية التي فيها دبل تتحول الى epoxid في الكبد
لذلك يجب عمل فحص للكبد عند استعمال الأدوية التي فيها دبل

هذا المركب في السجاير والبلاستيك

مسرطن


1
2
3
4
5
6
7
8
9
10
11
12
cytochrome P450
$O_2$
O
epoxid
$H_2O$
epoxide hydrolase
O
HO
HO
$O_2$
cytochrome P450
O
HO
HO

benzo[a]pyrene

4,5-benzo[a]pyrene oxide

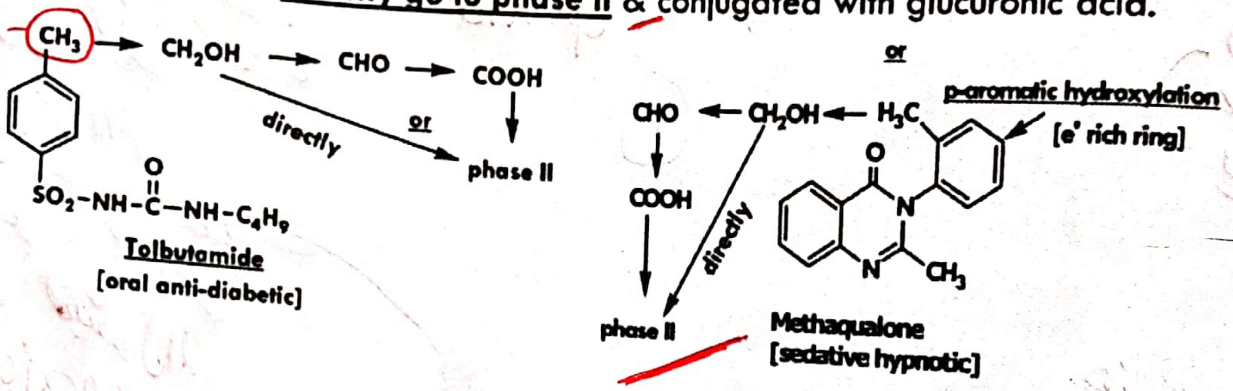
a diol epoxide

## ③ Oxidation at Benzylic carbon

- **Benzylic carbon** is C attached to aromatic ring.
- By oxidation → **alcohol [carbinols].**
- **1ry alcohol** → aldehyde → carboxylic acid **While 2ry alcohol** → ketone.
- **Alcohols** may **directly go to phase II** & conjugated with glucuronic acid.

مهم

اذا معانا الميثايل يتحول لا كحول اذا لا ينفع يتحول الى الدهيد الى حمض اذا المشبع يدخل phase II



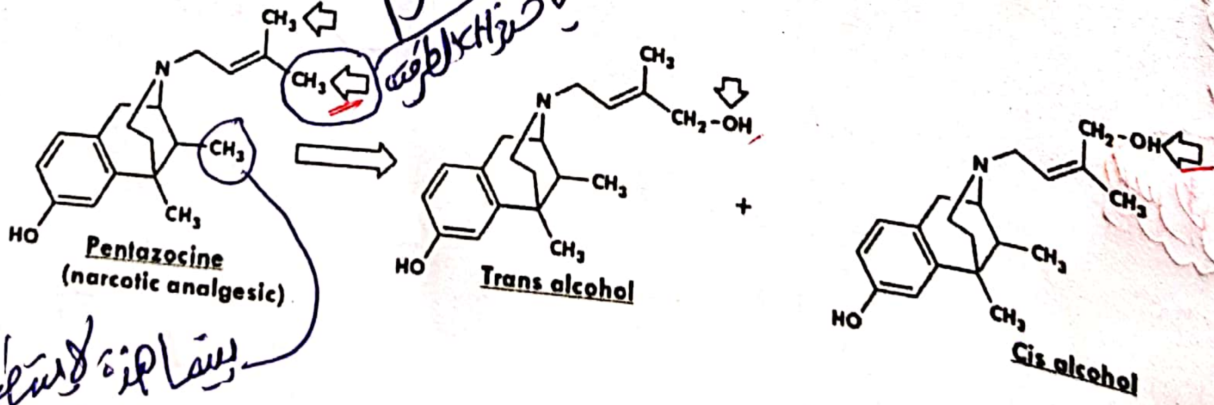
CH3
CH2OH
CHO
COOH
directly
or
phase II
O
SO2-NH-C-NH-C4H9
or
CHO
CH2OH
H3C
p-aromatic hydroxylation
[e' rich ring]
COOH
directly
O
N
N
CH3
phase II

**Tolbutamide**
[oral anti-diabetic]

**Methaqualone**
[sedative hypnotic]

وجود CH3 يسهل من خروج الدواء.

## ④ Oxidation at Allylic carbon



CH3
CH3
N
CH3
HO
CH3
N
CH3
CH2-OH
CH3
HO
CH3
+
CH2-OH
N
CH3
CH3
HO
CH3

يروح الانزيم يأخذ CH3 الطرفية

**Pentazocine**
(narcotic analgesic)

**Trans alcohol**

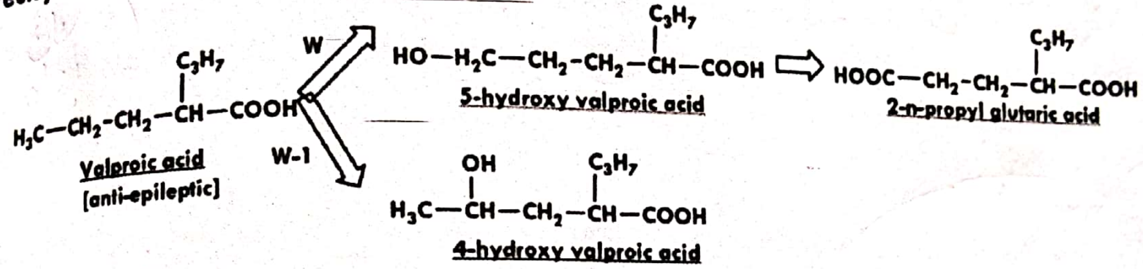
**Cis alcohol**

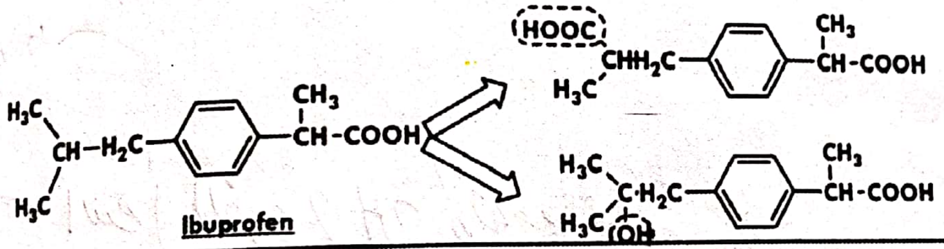
يهاجمة لايستطيع الانزيم بسبب الزحمة.
steriz

## ⑤ Oxidation of aliphatic carbons

**Aliphatic Carbons:**

- This oxidation commonly takes place in drug molecules with straight or branched alkyl chains.
- Alcohol metabolites formed → further oxidation to aldehydes & ketones. [Or directly conjugated with glucuronic acid].

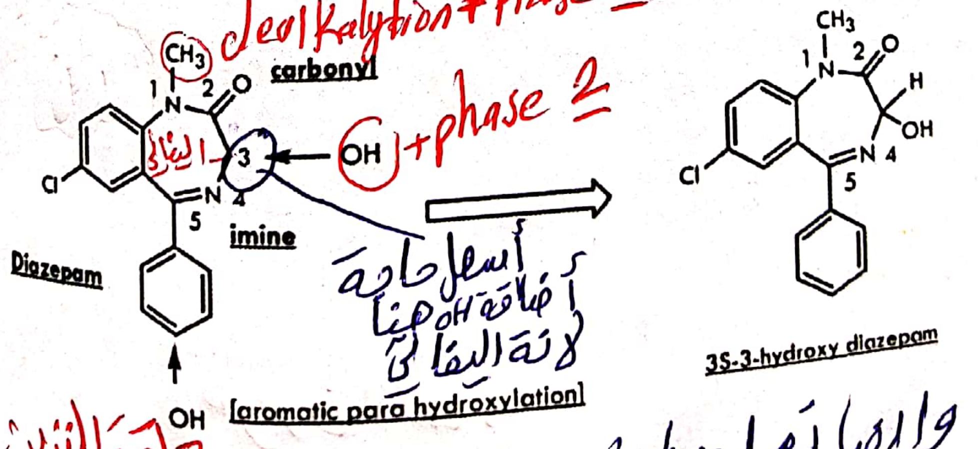

W
W-1
Valproic acid
[anti-epileptic]
5-hydroxy valproic acid
2-n-propyl glutaric acid
4-hydroxy valproic acid



مهم جداً

## ⑥ Oxidation of C atom α to carbonyl & imine

→ Give The metabolism ?


carbonyl
imine
Diazepam
[aromatic para hydroxylation]
3S-3-hydroxy diazepam

dealkylation + phase 2

OH + phase 2

اليفاتك

أسهل حاجة إضافة OH هنا لأنه اليفاتك

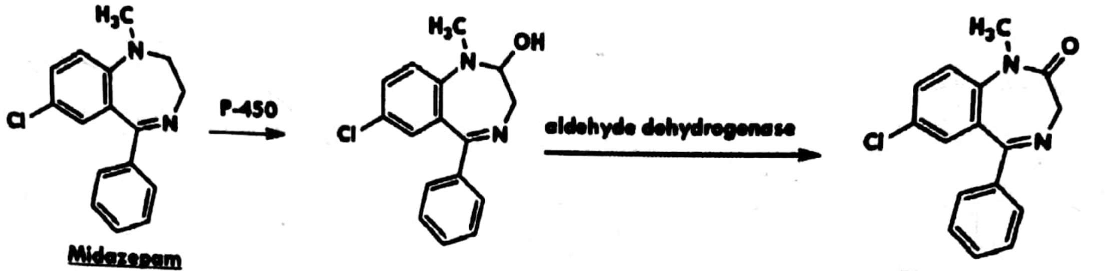
حلقة البنزين نعمل لها OH

والهيا تعمل phase 2 لأن المركب كبير حلقة سباعية وسداسية وكلور.

oH

# ⑦ Oxidation of alcohols & aldehydes

- Benzylic, allylic, aliphatic hydroxylation → alcohols [or carbinols intermediates].
- Alcohols formed → **direct conjugation** OR **further oxidized** to aldehydes [1ry alc.] or ketone [2ry alc.]
- **Aldehydes** comes from **alcohols** or **from oxidative deamination** [or 1ry amines] → **oxidation to carboxylic acid** derivative.
- 2ry alcohol → oxidation to ketone. This reaction may be reversed readily by alcohol dehydrogenase enzyme **[2ry alcohol are more polar, so more likely to be conjugated than ketone]**



**Midazepam**

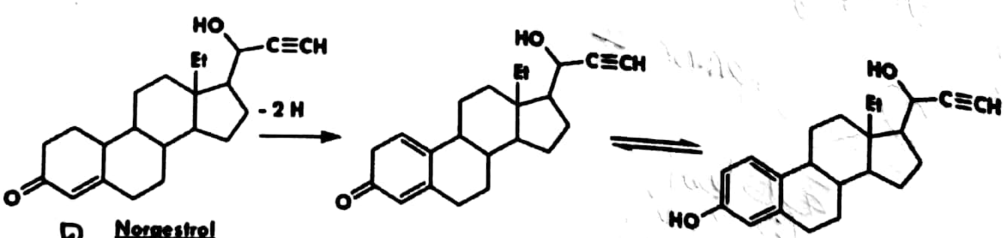
**Diazepam**

→ أسهل للخروج excretion، OH لاحتوائها acceptor & donor

بينما الكربونايل ع لا

# ⑧ Oxidative aromatization

- Alicyclic drug **dehydrogenated** to an aromatic metabolite.



**Norgestrol**

**17-alpha-ethinyl-18-homoestradiol**

هرمون الرجال

هرمون النساء

بواسطة انزيم الاروماتيز يقوم بتحويل هرمون الاندروجين الذكور[illegible]
إلى هرمون الاستروجين الانثوي ابو ٣ روابط.

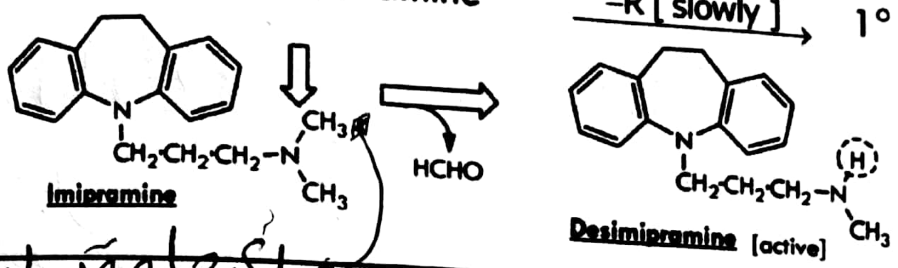
## Oxidation of Heteroatom-containing compounds

- [i] Hydroxylation of C directly attached to heteroatom [N,S or O] [        to it ]
- [ii] Direct attack on the hetero atom [ N or S but not O ]

# Oxidation of C-N systems

- The *α-carbon oxidation* is catalysed by cytochrome P-450 enzyme system. **There must be one H atom at least on this carbon.**

3° amine $\xrightarrow{-R\text{ [ Rapidly ]}}$ 2° amine $\xrightarrow{-R\text{ [ slowly ]}}$ 1° amine



CH3
CH2·CH2·CH2–N
CH3
HCHO
H
CH2·CH2·CH2–N
CH3

**Imipramine**

**Desimipramine** [active]

اي حاجة جنب ال N
شيلها واضيف H

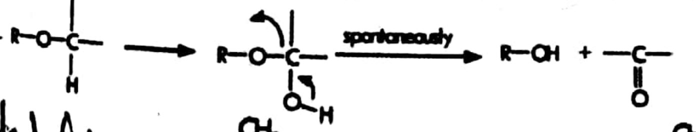
# C - O system

- Involves **O-dealkylation** & occurs mainly in **ethers**.
- Done by ***hydroxylation of C α to O*** → ***spontaneous cleavage*** of C-O bond → ***phenol or alcohol.***

deamethylation

- **Small alkyl gps rapidly O-dealkylated**. E.g. **Codeine.**

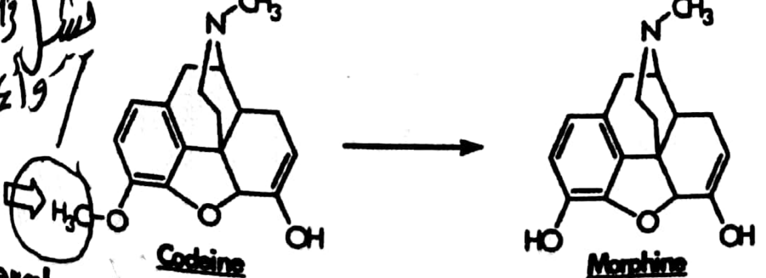
مهم
امتحان



R–O–C–
H
R–O–C–
OH
spontaneously
R–OH + –C–
O

methed → deallylation (sandt
Enzyme → cyto P_450
results → morphine

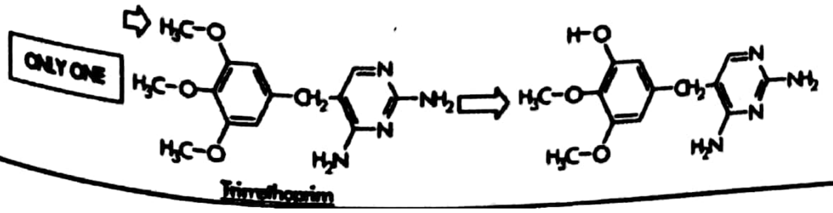
CH3 هشيل
واحط بدالها
H



N–CH3
H3C–O
OH
N–CH3
HO
OH

**Codeine** **Morphine**

- If **several non-equivalent methoxy** groups → selective dealkylation of **only one** methoxy. E.g. **Trimethoprim.**



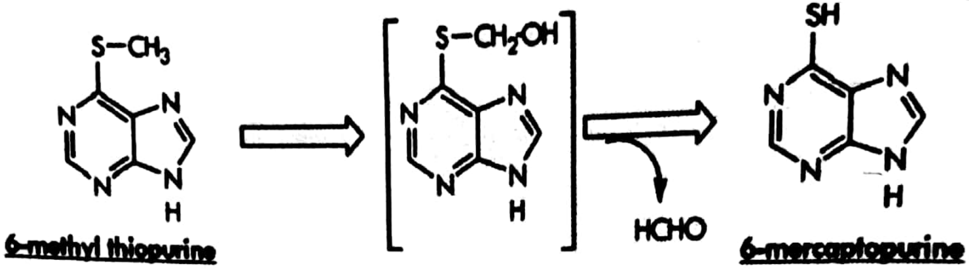
ONLY ONE
H3C–O
H3C–O
H3C–O
CH2
N
N
NH2
H2N
H–O
H3C–O
H3C–O
CH2
N
N
NH2
H2N

**Trimethoprim**

اي حاجة فيها S اشيل
ماعدا اذا كانت
ال S داخل الحلقة
نعملها اكسدة

# C - S systerms

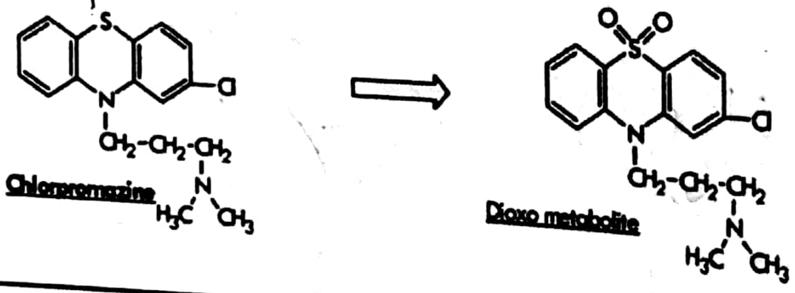
**1. S-dealkylation:**

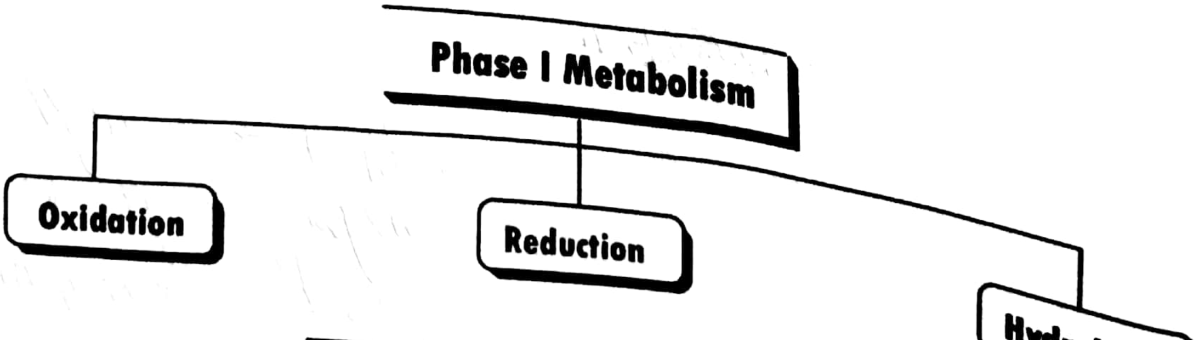

S—CH3
6-methyl thiopurine
S—CH2OH
HCHO
SH
6-mercaptopurine

**2. S-oxidation:**

•Give sulfoxide [S=O] → or further oxidation gives sulfone [O=S=O]

S داخل الحلقة نعملها اكسدة


Chlorpromazine
Dioxo metabolite



Phase I Metabolism

Oxidation

Reduction

Hydrolysis

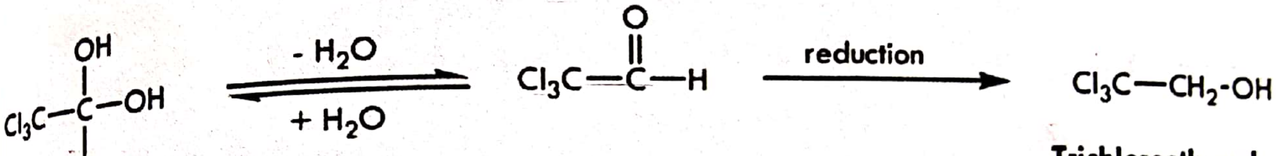
## [II] REDUCTION REACTIONS

إختزال تحويل الالدهيد الى كحول

# [II] REDUCTION REACTIONS

## [I] Reduction of Aldehydes & Ketones:

- Reduction of **aldehyde** → **1ry alcohol** [of **ketone** → **2ry alcohol**].
- Majority of aldehydes oxidized to carboxylic acids but may reduced to alcohols especially if attached to **e-withdrawing group**. [c.f. oxidation] Exmple:

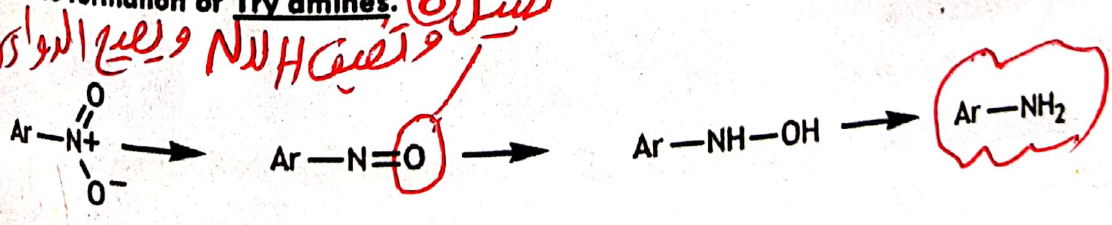

OH
$Cl_3C$–C–OH
H
- $H_2O$
+ $H_2O$
O
$Cl_3C$–C–H
reduction
$Cl_3C$–$CH_2$-OH

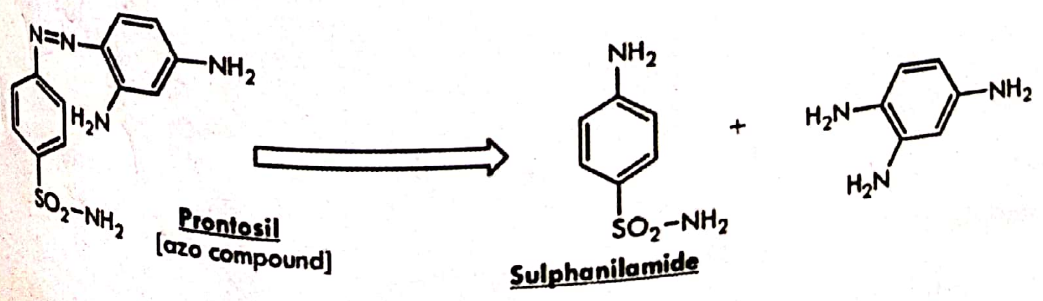
**Chloral hydrate** **Chloral** **Trichloroethanol** [active]

اي حاجة بها N نشيل ممكن نحول $NO_2$ الى $NH_2$
اشيل O واضيف H

## [ii] Reduction of Azo & Nitro compounds [to 1ry $NH_2$]:

- Leads to formation of **1ry amines.** نشيل O
وتضيف H لل N ويصبح الدوا potent


Ar–$N^+$(=O)–$O^-$
Ar–N=O
Ar–NH–OH
Ar–$NH_2$


N=N
$NH_2$
$H_2N$
$SO_2$–$NH_2$
$NH_2$
$SO_2$–$NH_2$
+
$H_2N$
$NH_2$
$H_2N$

**Prontosil** [azo compound] **Sulphanilamide**

**Phase I Metabolism**

- **Oxidation**
- **Reduction**
- **Hydrolysis**

## [III] HYDROLYTIC REACTIONS

- [i] **Ester Hydrolysis**
- [ii] **Amide Hydrolysis**

اذا أريد دواء يطلع سريع
أحط CH3
أحط استر.

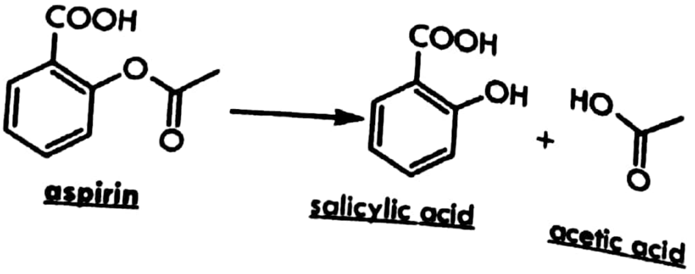
long duration
اذا اريد أطول الدواء
① أكبر ال chain
② اضيف مجموعات ساحبة
③ احول الاستر الى أميد

التأثير في الاستر ضعيف
لا يحتاج طاقة

سهل
سريع

## [i] Ester Hydrolysis:

- Catalyzed by **Esterases** which are non-specific & widely distributed in liver, kidney, intestine.
- Major pathway for esters → facile hydrolysis.
- Hydrolytic products are **alcohol & acid** → contain functional groups that can be conjugated.



[illegible]

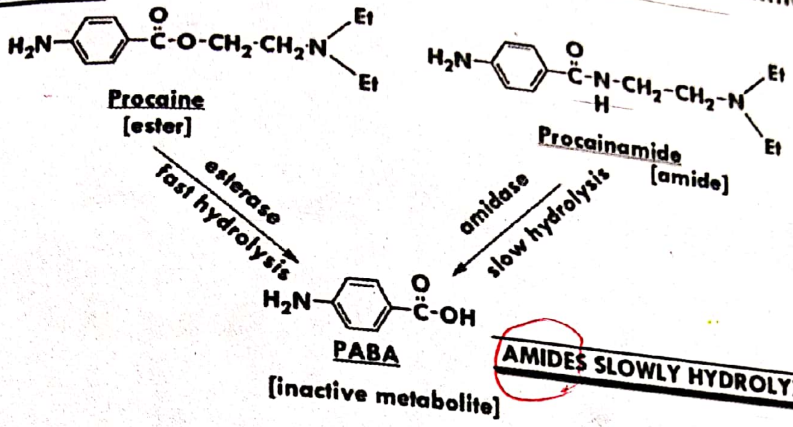
## [ii] Amide Hydrolysis:

- Catalyzed by **microsomal amidases.**
- Hydrolytic products are → **carboxylic acid & amine metabolites.**

- Catalyzed by **microsomal amidases.**
- Hydrolytic products are → **carboxylic acid & amine metabolites.**

**Ester hydrolysis is easy to occur → rapidly hydrolyzed > amide hydrolysis.**

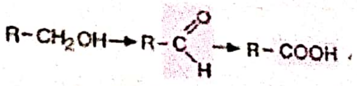
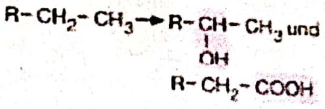
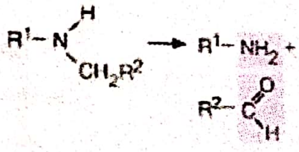
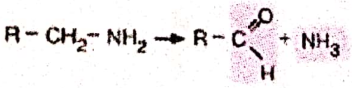
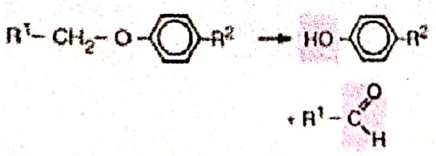
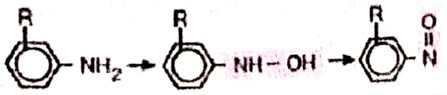
**Example :**



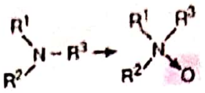
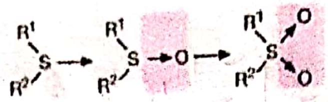
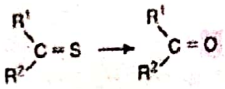
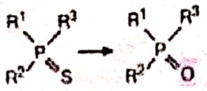
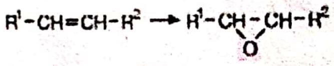
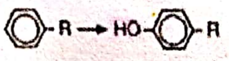
Procaine
[ester]
Procainamide
[amide]
esterase
fast hydrolysis
amidase
slow hydrolysis
PABA
[inactive metabolite]

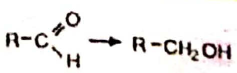
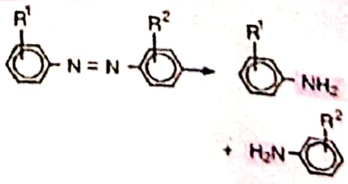
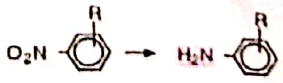
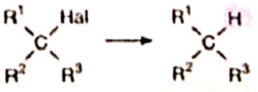
AMIDES SLOWLY HYDROLYZED THAN ESTERS

الخلاصة

| Reaction | Chemical modification | Examples (substrates) |
|---|---|---|
| **Oxidations** | | |
| Oxidation of alcohols and aldehydes |  | Benzyl aclohol<br>Pyridoxine |
| Oxidation of aliphatic chains |  | Barbiturates |
| Oxidative N-dealkylation |  | Ephedrin<br>Lidocaine<br>Methamphetamine |
| Oxidative deamination |  | Fomocaine<br>Histamine<br>Mescalin<br>Noradrenaline |
| Oxidative O-dealkylation |  | Codeine<br>Mescalin<br>Papaverin<br>Phenacetin |
| Oxidation of aromatic amines |  | Anilin derivatives |

Biotransformation pathways of drugs, phase-I reactions

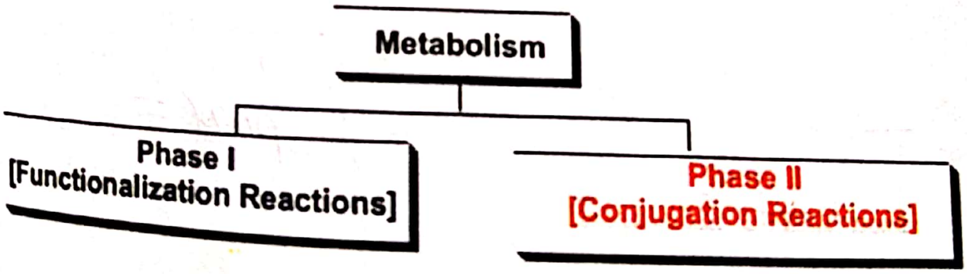
| Reaction | Chemical modification | Examples (substrates |
|---|---|---|
| **Oxidations** | | |
| N-Oxidation |  | Imipramine |
| S-Oxidation |  | Phenothiazines |
| Desulfation |  | Thiobarbiturates |
| |  | Parathion |
| Epoxidation |  | Aldrin<br>Carbamazepine |
| Hydroxylation of aromates |  | Chlorpromazine<br>Phenobarbital<br>Propranolol |

| Reaction | Chemical modification | Examples (substra |
|---|---|---|
| **Reductions** | | |
| of aldehydes |  | Chloralhydrate |
| of azo compounds |  | Salazosulfapyridine |
| of nitro groups |  | Nitrazepam |
| Dehalogenation |  | Halothane |

# Drug Metabolism
## 2
## Medicinal Organic Chemistry
## and
## Drug Design
By
**Ass Prof .Mokhtar Al-Ghorafi**

---

# Drug Metabolism



Metabolism

Phase I
[Functionalization Reactions]

Phase II
[Conjugation Reactions]

ليس كل الأدوية التي تدخل phase 1 تخرج و
انما فيه بعض الأدوية high lipophilic تدخل phase 1 وتفضل في phase 2

# Phase II Reactions

- Metabolites from phase I NOT always hydrophilic or pharmacologically inactive.
- So, they enter phase II to produce conjugated products which have the following properties:

صو
مواصفات الدواء الذي يدخل phase 2

1. More polar.
2. More soluble in water.
3. Readily excretable.
4. Biologically inactive.
5. Non-toxic.
6. NON-metabolite

# Phase II Reactions

تقسم الى عدة

- Phase II includes:

أكثر شائع 1
- ① Conjugation with glucuronic acid [Glucuronidation].
- ② Conjugation with sulphate.
- ③ Conjugation with amino acids.
- ④ Conjugation with glutathione.
- ⑤ Acetylation.
- ⑥ Methylation.

} phase 2

- الجلكوز يتأكسد الى حمض الجلوكورنيك
- الكبد يأكسد الجلوكوز الى Glucuronic acid

حمض ذوبانيته أعلى ~~فعالية~~ من السكر لأن الحمض
مثلا ين – ع ذوبانية تكون أعلى بكثير

## 1.Conjugation with glucuronic acid [Glucuronidation].

حمض Glucuronic يعتبر الأكثر شيوعا لأن السكر موجود بكميات كبيرة في اجسامنا

**•The major & most common route of conjugation reactions due to:**

1.Glucuronic acid derived **from D-glucose** **[readily available** in body].

**2.Large number of functional groups** [phenols, alcohols, carboxylic acids & amines] → can combine enzymatically with glucuronic acid.

3.Formed glucuronides → **water soluble** → rapidly eliminated.

Mechanism of glucuronidation:[two steps]

**Mechanism of glucuronidation:[two steps]**

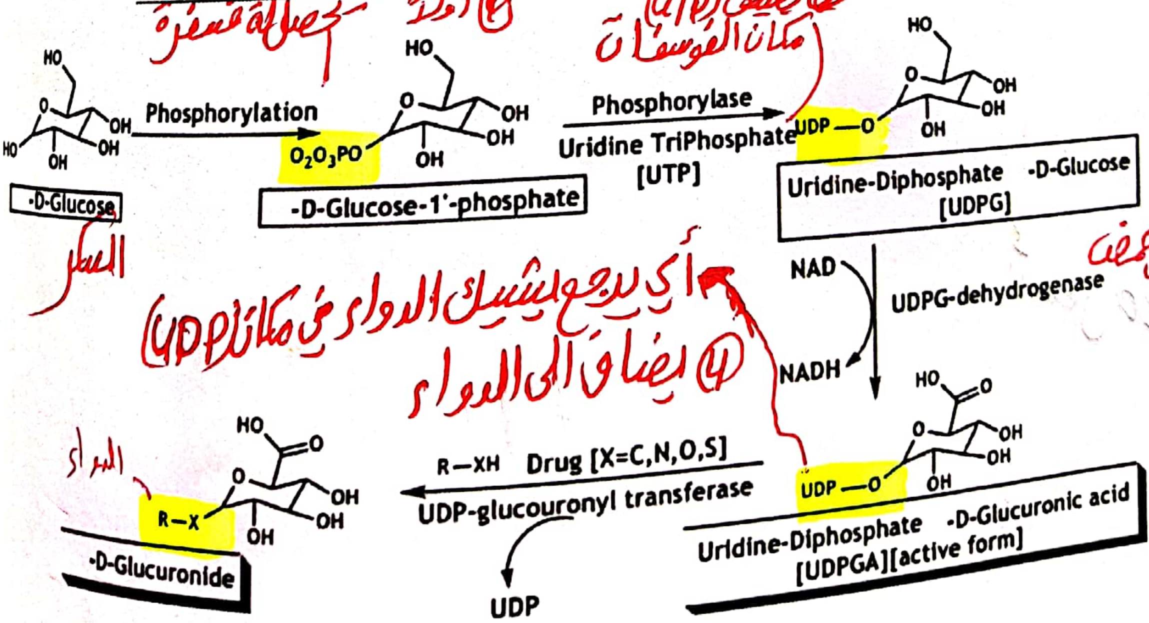
•Activation of glucuronic acid to **Uridine Diphosphate Glucuronic Acid** [UDPGA].

•Condensation of the drug [or phase I metabolite] with this active form.

The reaction is catalyzed by **UDP-glucuronosyl transferase enzyme**

اي دواء يدخل phase 2 يكون Long duration
: Long action.
ليس بكل سهولة تحصل له اخراج

**Mechanism of glucuronidation:[two steps]**


HO
O
OH
HO
OH
OH
-D-Glucose
Phosphorylation
$O_2O_3PO$
-D-Glucose-1'-phosphate
Phosphorylase
Uridine TriPhosphate
[UTP]
UDP —O
Uridine-Diphosphate -D-Glucose
[UDPG]
NAD
UDPG-dehydrogenase
NADH
UDP —O
Uridine-Diphosphate -D-Glucuronic acid
[UDPGA][active form]
R—XH Drug [X=C,N,O,S]
UDP-glucouronyl transferase
UDP
R—X
-D-Glucuronide

① أولا تحصل له فسفرة

② نضيف (UTP) مكان الفوسفات

③ يتأكسد الحمض

④ يضاف الى الدواء

أي يرجع يشيل الدواء في مكان (UDP)

السكر

الدواء

**Glucuronidation NOT occur by D-glucuronic acid, it must be activated 1st to UDPGA'**

نادرة
تقسيم الدواء معالج بالسكر الى C ، S ، N ، O

# Types of Glucuronides:

## [i] O-Glucuronides

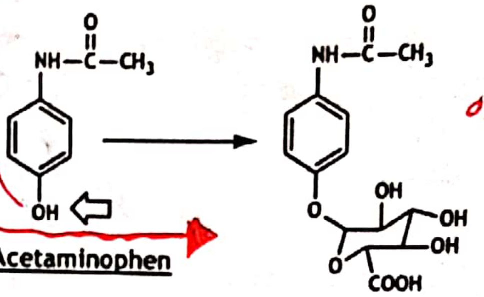
### 1. Ether glucuronides: [Alcohols/ Phenols]

$H_2O$

OH

OH

الدواء معه OH
والسكر معه OH
نشيل من هنا نشيل OH
من السكر و H من الدواء
وربطنا



Acetaminophen

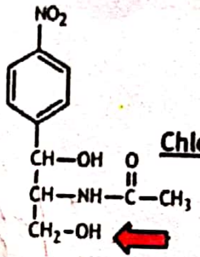
O-Glucuronide

الدواء مع OH
والسكر معه OH
لازم الدواء يكون عنده H علشان ناخذه OH
من السكر و H من الدواء
وشبكنا السكر
phase 2

⇩

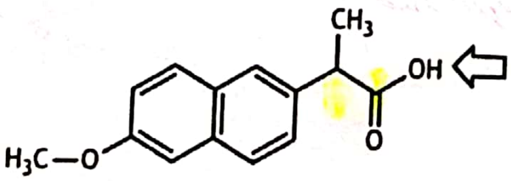
$Cl_3C—CH_2—OH$

Trichloro ethanol
[metabolite of chloral hydrate]



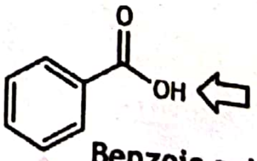
Chloramphenicol

### 2. Acyl glucuronides [Aliphatic & aromatic carboxylic acids] → Esters



Naproxen

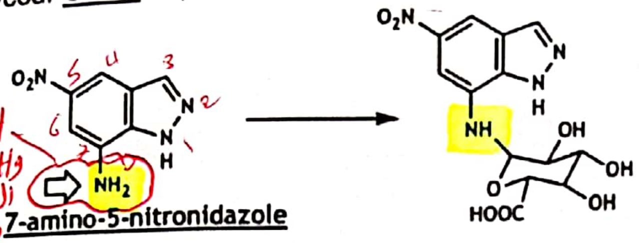
أسهل ه جاهز



Benzoic acid

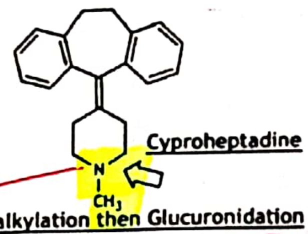
## [ii] N-Glucuronides

- For aromatic amines, alkyl amines, amides, crabamates & non-aromatic nitrogenous heterocycles.
- Occur **ONLY** in primary and secondary amines.**[3ry amine must be dealkylated 1st]**


O₂N
N
N
H
NH₂
5
4
3
2
1
6
7
O₂N
N
N
H
NH
OH
OH
OH
O
HOOC

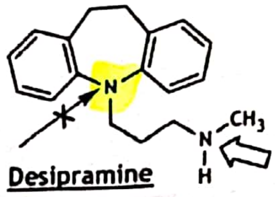
**7-amino-5-nitronidazole**

الـH من الـN
ونحط مكانه
السكر
وكملنا



**Cyproheptadine**

**Dealkylation then Glucuronidation**



**Desipramine**

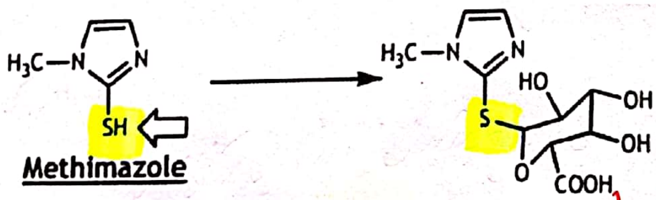
اذا كانت N مشبوكة مع كربون ذات CH3
① نبدأ نعمل اولاً phase 1
بعدين نرجع نعمل phase 2

---

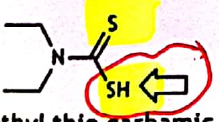
اذا معطى S / نفس الشي نشيل

## [iii] S-Glucuronides

For **drug with thiol group [SH].**

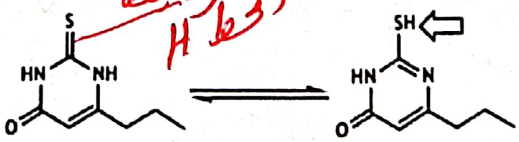

H₃C—N
N
SH
H₃C—N
N
S
HO
OH
OH
O
COOH

**Methimazole**



**N,N-diethyl thio carbamic acid**

نكسر الرابطة ونحط H


S
HN
NH
O
SH
HN
N
O

**Propyl thiouracil**

**If disulfide [-S-S-] → reduction 1st to make –SH → then conjugation with glucuronic acid**

اذا معطى S-S نكسر

وكذلك اذا كان معطى N-N

الكربونة بتكون نادرة ما بتشبك الكبد معاها.

في الأغلب NOS
تشبيكها للكربون نادرة
إلا إذا كان معاك مجموعتين
ساحبتين من الطرفين.

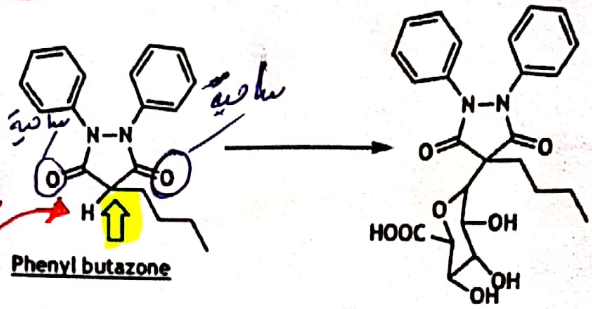
## [iv] C-Glucuronides

•Substances with 1,3-dicarbonyl structure → ↑ acidity of methylene C → C-glucuronide. [as **phenylbutazone**]

ممكن الدواء يشتبك بسكر مع الكربونة إذا كانت الكربونة جنبها كربونايل من الجهتين

إذا عندك مجموعتين ساحبتين من الأطراف بستطيع أن أشيل من النص H

من كثر السحب تقوم الكربونة كطرد H



Phenyl butazone

أشيل دوائي وأحط له $SO_3$

يقوم الكبد يحط $SO_3$ على OH، NH

لا يضيف على SH أو COOH

في الامتحان أقول لك أي المركبات التالية يحصلها conjugation with $SO_3$

OH , NH

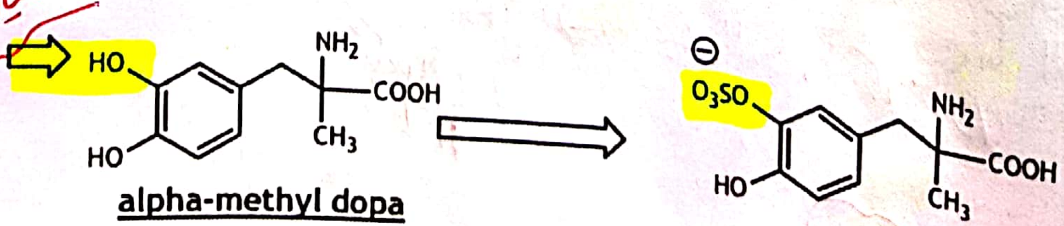
## [2] Sulfate Conjugation

أعلى جهد الكهروسلبية تستعمل $SO_3$

أكثر الـ $SO_3$ تستعمل على المركبات الطبيعية

•**Mainly for drugs with –OH or –NH** [alcohols, phenols, aromatic amines, N-hydroxyls] → so, important reaction in metabolism of steroids, catecholamines, thyroxine & bile acids.

•Usually ↑ water solubility & drug excretion [that pka of sulfonate group is 1-2]



alpha-methyl dopa

* الامينات يتم اعمل لها Glucuronidation مع Glucourinc acid ✓
SO3 ✓
amino acid مع

الانواع اللي تحتاج

لكن الامينات لا تفعل يا دكتور

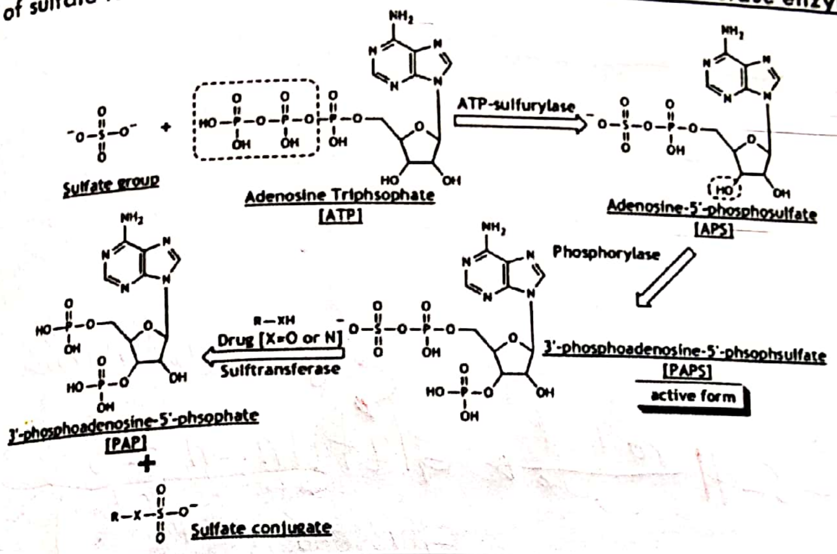
الامينات عايزة عمل SO3 with glucorinc acid

Glucorine acid
amino acid مع الحامضي الـ OH

أما SO3 لل NH و ال OH

## Mechanism:[two steps]

- Inorganic sulfate **must be activated 1st to 3-phospho adenosine-5'-phosphosulfate [PAPS].**
- Transfer of sulfate to drug or drug metabolite [catalyzed by **Sulfotransferase enzyme**]



Sulfate group
Adenosine Triphsophate
[ATP]
ATP-sulfurylase
Adenosine-5'-phosphosulfate
[APS]
Phosphorylase
3'-phosphoadenosine-5'-phsophsulfate
[PAPS]
active form
R—XH
Drug [X=O or N]
Sulftransferase
3'-phosphoadenosine-5'-phsophate
[PAP]
+
Sulfate conjugate

قديما أخذ الكبد حمض اميني من جسمك ويشبكه مع السم (الدواء) ويخرجه

يشيل الدواء بحمض اميني ويخرجه

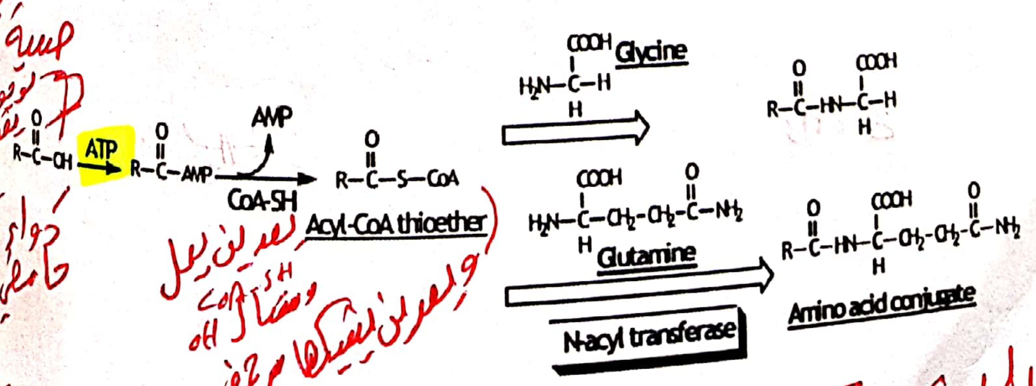
## [3] Amino Acids Conjugation

(الادوية التي يشبك معاها [illegible])

- Most common amino acids used in conjugation are **GLYCINE**, **GLUTAMINE**.
- It **needs activation of drug-COOH** → as acyl Co-A **[EXCEPTION]**

## Mechanism:[two steps]

- Activation of carboxylic acid group of drug substrate **to highly reactive acyl-CoA.**
- Transfer of activated drug to the amino acid, **catalyzed b N-acyl transferse enzyme.**



ATP
AMP
CoA-SH
Acyl-CoA thioether
Glycine
Glutamine
N-acyl transferase
Amino acid conjugate

عشان نكسر لوجود الرابطة يتفعل ATP

دواء حامضي

بعدين يشيل CoA-SH ومشال OH

وبعدين يشبكها مع حمض

الادوية الحامضية يتم اخراجها عن طريق (amino acid)

Glucuronidation

SO3 X

الكحول والاسيتامينوفين ← تحتوي على Free radicals

الـ Free radicals في alcohol يقوم
الـ Glutathione يتأكسد الى يقوم
Glucose-6-phosphate يرجعه الى الوضع
الطبيعي

## 4] Glutathione or Mercaptouric Acid Conjugation

•Important pathway for **DETOXIFICATION** of chemically reactive electrophilic compounds by nucleophilic SH group [that may cause protein & nucleic acids damage].

GSH is **tripeptide**: **[γ-glutamyl cysteinyl glycine]** found in most tissues

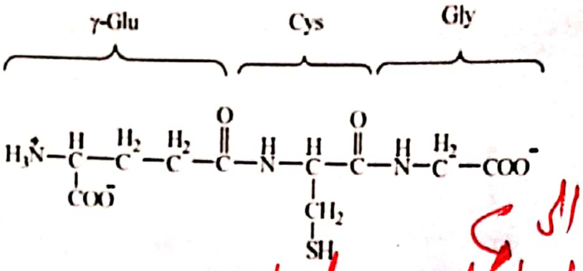


Figure 59.: the structure of glutathione

عندما يتأكسد يتحول الى

$$\text{Glutathione-SH} \xrightarrow[\text{مؤكسد}]{\text{radical}} \text{Glutathion} = S$$

جزيء اخر

(جلوتاثيون مؤكسد)

$$\text{Glutathione-SH} \leftarrow \text{Glucose-6-phosphate dehydrogenase}$$

يقوم يرجعه الى وضعه الطبيعي

Liver - سيلمارين تعمل تدعيم للكبد

تحويل الدواء من less polar الى high polar

في الاستقلاب نحول العكس من high polar الى less polar

معنى ذلك تضيف $\overset{O}{\overset{\|}{C}}-CH_3$ يحول الدواء من high الى less

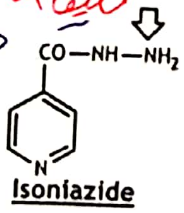
لكن ما زال الدواء قابل

## ⑤ Acetylation

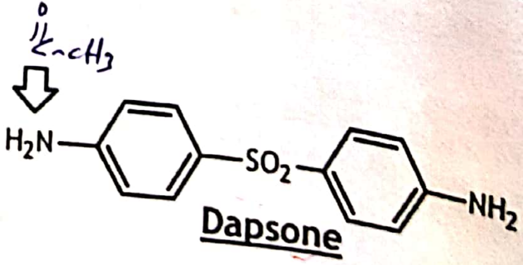
•Very important pathway for drugs with **1ry amino group** [aromatic amines, hydrazines, hydrazides, aliphatic amines]

تضيف هنا $\overset{O}{\overset{\|}{C}}-CH_3$ في الـ استيل

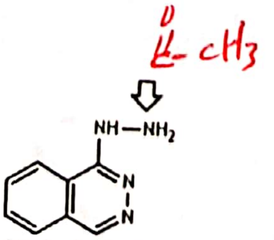
لتقليل السمية عليه



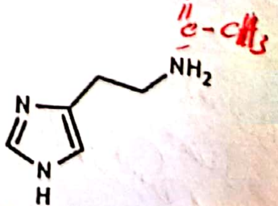
**Isoniazide**



**Dapsone**



**Hydralazine**



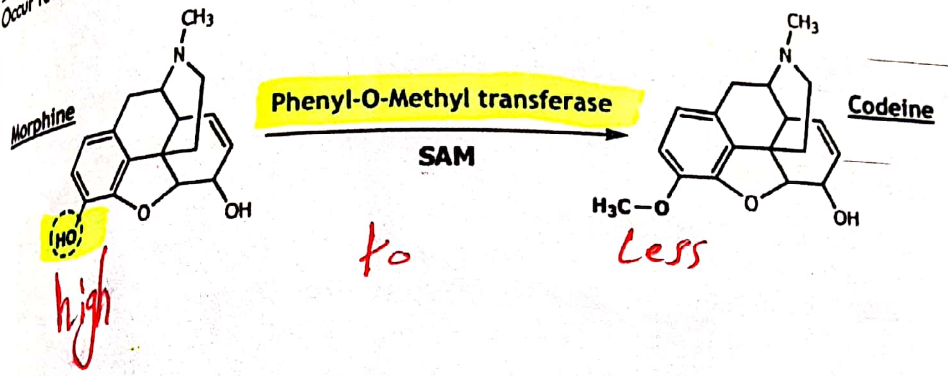
**Histamine**

high ال low وبتحول الدواء من
Phenyl-o-methyl تتم عن طريق
بواسطة الانزيم

# ⑥ Methylation

•Minor pathway in drugs metabolism, but **very important in biosynthesis & metabolism of endogenous substances [Catecholamines]**.

Occur for compounds **with OH group**



الديزيام مع القات ← ما يرقدكش

الاطفال في الاشهر الاولى phase 2 غير موجودة عندهم وتماطوش

## Factors affect drug metabolism:

**[1] Age:**

•Deficiency of microsomal enzymes in **newborn child** → prolongation of action & diverse reactions of some drugs. E.g. **Chloramphenicol**.

النساء

لأن الديزيبام في النساء يصبح مفعوله أكثر من الرجال بسبب النساء عندهن adipose tissue أكثر وبالتالي يخزن ويفضل كثيرا

**[2] Sex differences:**

Rate of metabolism of some drugs are **faster in male > females.** E.g. **Diazepam**

### [3] Physiologic or disease state:

•**Diseases alter liver function** → affect metabolism rate.

العوامل الوراثية

**[4] Genetic factors:**

- **Absence of special gene** responsible for synthesis of enzymes essential in normal metabolism → metabolic disorders [affect intensity & duration of the drug].

اذا كان الدوا high lipophilic فيحصل له سكر ويخرج بواسطة biliary -
less يخرج مع البول

### [5] Inhibition of drug metabolism:

•Inhibition of enzymes responsible for metabolism of a drug → prolongation of its duration → toxicity.

E.g. **Cimetidine** inhibit Cyp-450 enzyme

### [6] Induction of drug metabolism:

•Induction of enzymes responsible for metabolism of a drug → ↓ duration → needed to be taken in **higher doses**.

•E.g. **Phenobarbitone** & **Alcohols** → ↑ level of Cyp-450 [chronic alcoholists need higher doses of sedatives].

### [7] Chemical structure & Stereoisomerism:

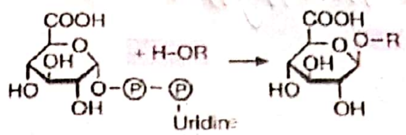
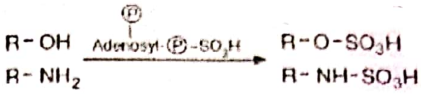
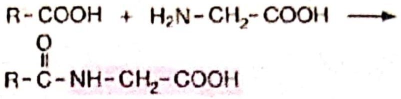
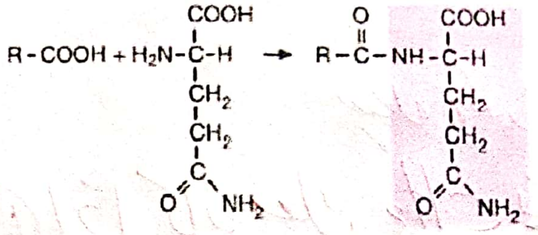
•**Procaine** & **Procainamide** → differ in their metabolism.

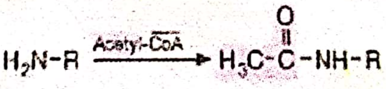
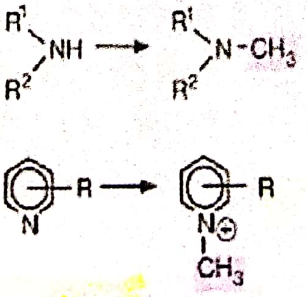
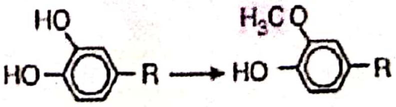
**(-)Hexobarbitone** & **(-)Warfarin** → metabolized **faster** than their (+) isomers

### [8] Species & Strain differences:

•**Amphetamine** → metabolized by either oxidative deamination or aromatic hydroxylation.

•**In man** → oxidative deamination is major **While in rats** → aromatic hydroxylation is major.

| Reaction | Chemical modification | Examples (substrates) |
|---|---|---|
| **Conjugations** | | |
| with activated glucuronic acid |  | Alcohols<br>Amines<br>Phenol |
| with activated sulfate |  | Aromatic amines<br>Phenols<br>Sulfonamides |
| with glycine |  | Benzoic acid<br>Isonicotinic acid<br>(as metabolite of isoniazide) |
| with glutamine |  | Indolylacetic acid<br>Phenylacetic acid |

| Reaction | Chemical modification | Examples (substrate |
|---|---|---|
| **Conjugations** | | |
| with activated acetic acid |  | Isoniazide<br>Sulfonamide |
| N-Methylation (with adenosyl methionine) |  | Methadon<br>Nicotinamide<br>Noradrenaline |
| O-Methylation (with adenosyl methionine) |  | Catecholamines |

الذي كان يتكسر سريع في عملية الايض هنا نخليه قوي

resistance To metabolism

دواء يتزال مفعول الدواء

# Metabolic Stabilization

لما

convert the drugs from high metaboliz to less metab

دواء بيتكسر بسرعة [illegible] دواء [illegible] ٣ مرات يومية

- Achieved by replacing a *labile group* with another, less or non-reactive moiety, provided this change is not detrimental to PD activity.

**Yielding unmetabolized drugs**

صعب يتكسر

سهلة الأكسدة

القاعدة الاولى ① اذا كان معك $CH_3$ نبعدها $CH_3$ ونخلي بدلها $CF_3$

② اذا كان معك استر نحوله أميد

# Metabolic Stabilization cont..

This could be achieved by:

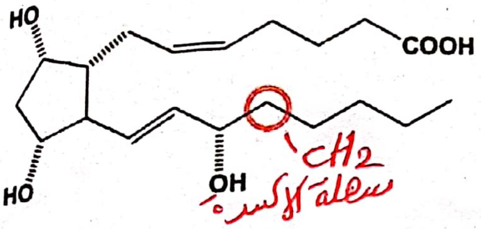
- ① Replacement of a $-CH_2-$ group with a $-C(CH_3)_2-$ or a $-CF_2-$ group
- ② Introduction of an N-*tert*-butyl group to prevent N-dealkylation
- ③ Inactivation of aromatic rings towards oxidation by substituting them with strongly electron-withdrawing groups (e.g., $CF_3$, $SO_2NH_2$, $SO_3^-$)
- ④ Replacement of a labile ester linkage with an amide group
- ⑤ Protection of the labile moiety by steric shielding

① اذا كان معك مركب فيه $CH_2$ استبدلها بـ $CF_3$ او $C(CH_3)_2$

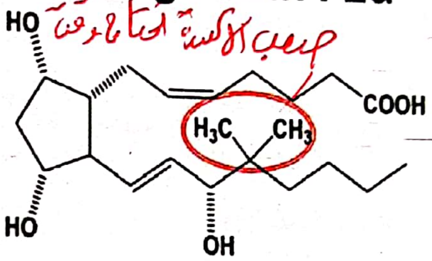
## Metabolic Stabilization cont..

- Replacement of a $-CH_2-$ group with a $-C(CH_3)_2-$ or a $-CF_2-$ group

**Prostaglandin F2α**


HO
COOH
HO
OH
CH2
سهلة الاكسدة

**16,16 dimethyl Prostaglandin F2α**


HO
صعب الاكسدة احتاج وقت
COOH
$H_3C$
$CH_3$
HO
OH

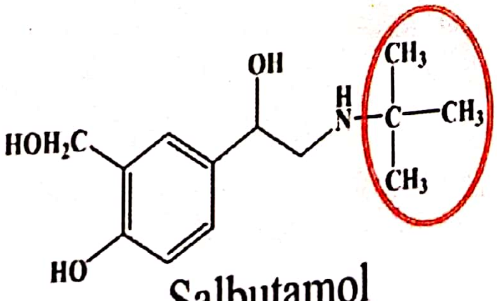
The dimethyl subsituent blocks the inactivation of the prostaglandins by blocking the oxidation of alc. OH to the Ketone, and so has longer half-life in man.

② اذا معك NH هنا لاتشيل كبرها خليها عريضة $N(H)-C(CH_3)_3$
خليها bulky صعب على الانزيمات تشيلها.

## Metabolic Stabilization cont..

- Introduction of an N-tert-butyl group to prevent N-dealkylation

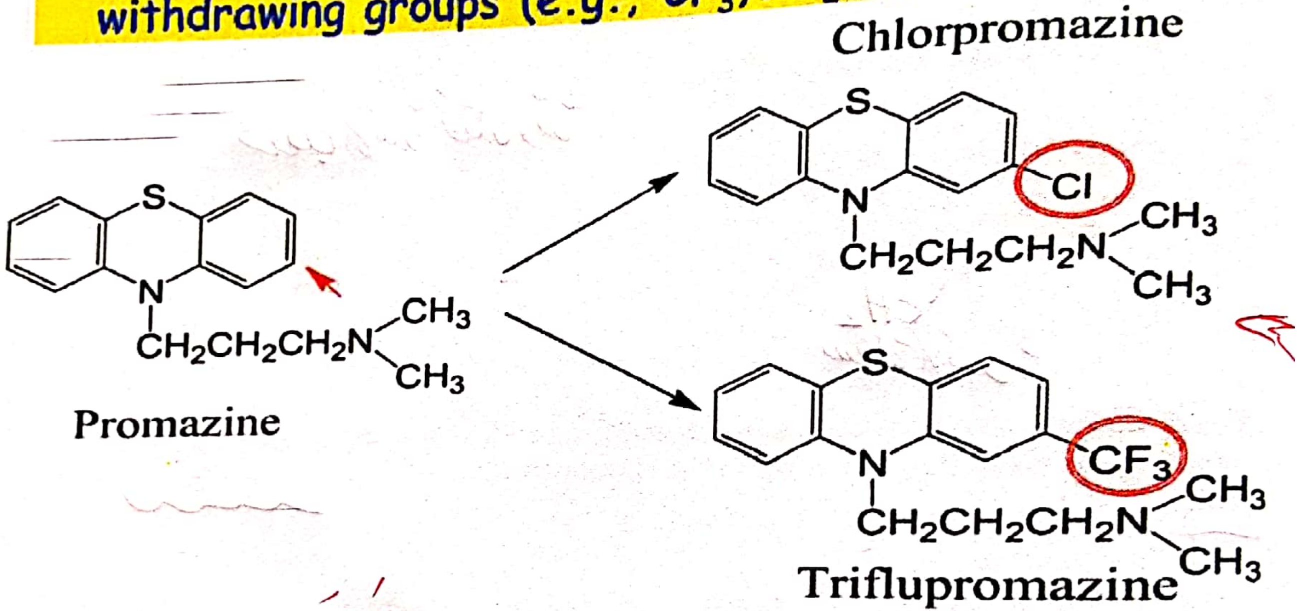
يعني لما كانت N خليها $N-C(CH_3)_3$ N-tert


OH
H
N
$CH_3$
C
$CH_3$
$CH_3$
$HOH_2C$
HO

Salbutamol

# Metabolic Stabilization cont..

- Inactivation of aromatic rings towards oxidation by substituting them with strongly electron-withdrawing groups (e.g., $CF_3, SO_2NH_2, SO_3^-$)


Chlorpromazine
S
N
Cl
$CH_2CH_2CH_2N$
$CH_3$
$CH_3$
Promazine
Triflupromazine
$CF_3$

معوض
④ اذا كانت عملي حلقة ومعاها مجموعة [illegible] ← اعطيها مجموعة ساحب
(CF3 or SO2, NH2, NO2) ليصبح دوا (long duration)
عشان الانزيمات العمل اي تحولها فقط

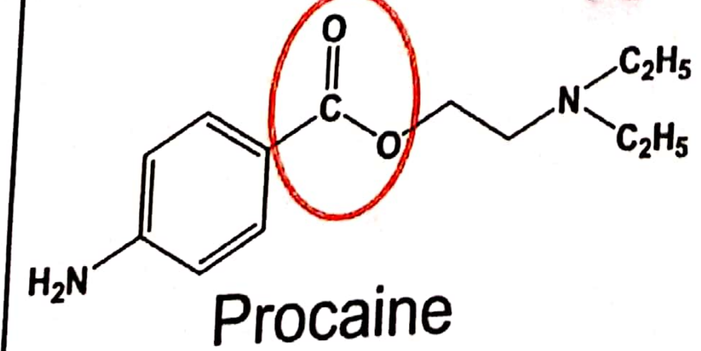
# Metabolic Stabilization cont..

اذا كان معي استر حوله الى اميد

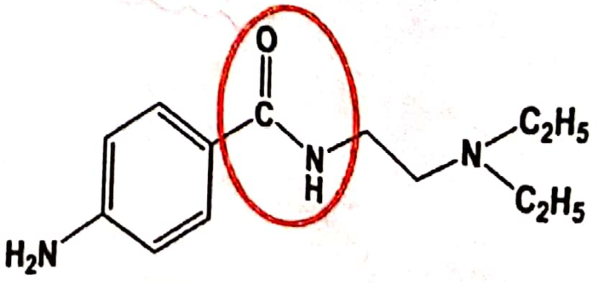
- Replacement of a labile ester linkage with an amide group

Ester

amide

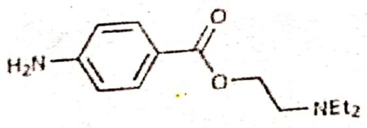


Procaine

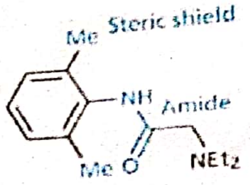


Procainamide

**For example, procaine is a good local anaesthetic, but it is short-lasting because its ester group is quickly hydrolyzed.**
**Changing the ester group to the less reactive amide group reduces chemical hydrolysis.**
**Furthermore, the presence of two -methyl groups on the aromatic ring helps to shield the carbonyl group from attack by nucleophiles or enzymes.**
**This results in the longer acting, local anesthetic lidocaine.**

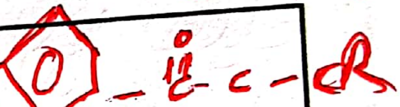


Procaine

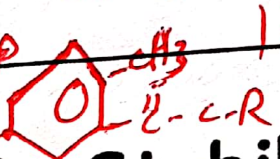

Me
Steric shield
NH
Amide
Me
O
NEt₂

Lidocaine

لو كانت مجموعة لها القدرة على الكسر بسرعة أعمل لها أعاقة
مثلاً اذا كانت



سهل الكسر للانزيم / لكن اذا



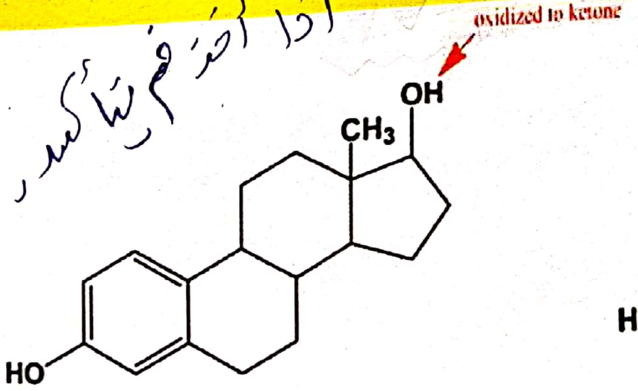
هنا اعاقة فراغية بيكون صعب كسره

# Metabolic Stabilization cont..

أحط مجموعات بجانب المجموعات القابلة للكسر بحيث تشتغل موانع

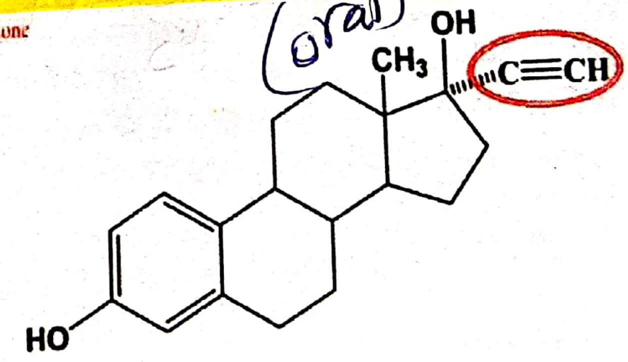
## Protection of the labile moiety by steric shielding

اذا أخذ فموياً بتكسر


oxidized to ketone
OH
CH₃
HO

**Estradiol**

(oral)


OH
CH₃
C≡CH
HO

**17 α-ethinyl Estradiol**

he ethinyl group blocked the oxidation of the 7ß- hydroxy group to ketone

سؤال امتحان ؛ How can you stabiliz
كيف تزيد مفعول الدواء

# Metabolic Stabilization cont..

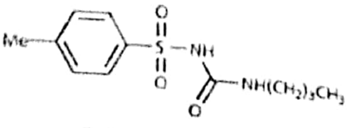
## ADVANTAGES

- Longer half-lifes
- Decreased possibilities of drug interactions
- Decreased inter- and intra-patient variability
- Decreased species differences
- Decreased number and significance of active metabolites

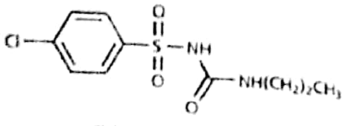
## Metabolic blockers

On the same lines, a popular method of protecting aromatic rings from metabolism at the para-position is to introduce a fluoro substituent. For example, CGP

an anticancer agent and was found to undergo oxidative metabolism at the para-position of the aromatic rings. Fluoro-substituents were successfully added to block this metabolism and the analogue CGP 53353 was also put forward for clinical trials.



Tolbutamide



Chlorpropamide